Temporary stereocentres for the asymmetric synthesis of chiral aldehydes

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Temporary stereocentres for the asymmetric synthesis of chiral aldehydes

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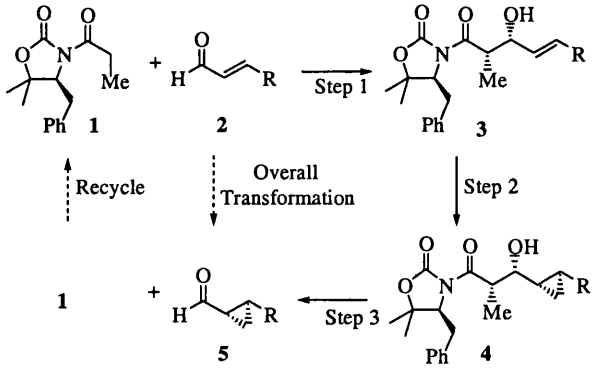
Abstract

Chiral aldehydes are versatile intermediates in natural product synthesis. This thesis describes a new three-step strategy that combines oxazolidin-2-one chiral auxiliaries and substrate directable reactions in a novel manner for the asymmetric synthesis of chiral cyclopropyl aldehydes (**Scheme 1**). This protocol utilises the stereoselective aldol reaction to *reversibly* generate a stereogenic *β*-hydroxyl centre (**Step 1**). This new 'temporary' hydroxyl group then carries out a substrate-directable cyclopropanation reaction to afford a cyclopropane aldol (**Step 2**). Cleavage *via* an anionic *retro*-aldol reaction regenerates the chiral auxiliary and an enantiopure cyclopropane carboxaldehyde (**Figure 1**) in excellent de and high yield (**Step 3**).



Step 1: 9BBN-OTf, $^{i}Pr_2NEt$, CH_2Cl_2, -78-0°C; 76-87% Yield, >95% d.e.
Step 2: Et_2Zn, CH_2I_2, CH_2Cl_2, -10-0°C; 89-99% Yield, >95% d.e.
Step 3: LHMDS, Toluene, 5°C; 51-75% Yield; >95% d.e.

Scheme 1

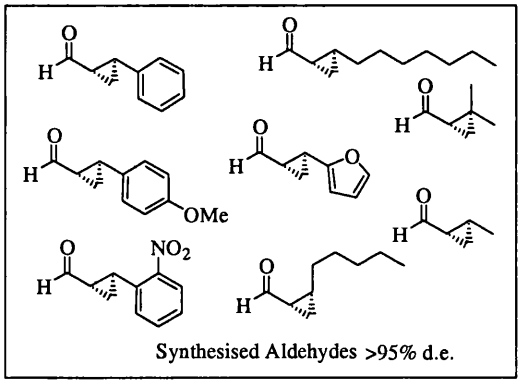
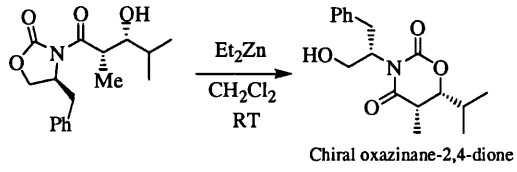
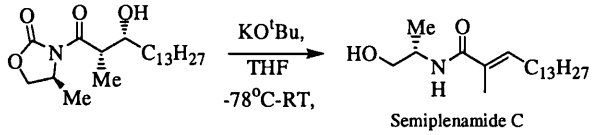


Figure 1

In contrast, simple Evans' auxiliaries failed to cleave under the same anionic *retro*-aldol conditions. The phenylalanine derived *syn*-aldol underwent a novel rearrangement reaction to afford a chiral 1,3-oxazinane2,4 dione when treated with a catalytic amount of diethyl zinc (**Scheme 2**). Alternatively, treatment of alanine derived *syn*-aldol with potassium *tert*-butoxide resulted in a novel elimination reaction to afford the α,β-unsaturated amide natural product, *Semiplenamide C* (**Scheme 3**).

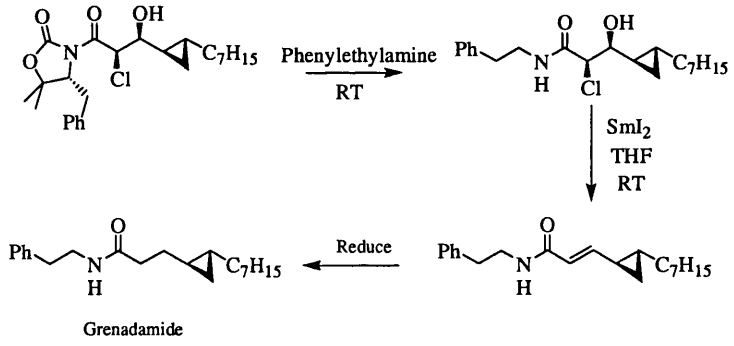


Scheme 2



Scheme 3

The principle of this temporary stereocentre methodology was then further explored through the asymmetric synthesis of the cyclopropane containing natural product, Grenadamide (**Scheme 4**). Cleavage of the oxazolidin-2-one fragment of the α-chloro cyclopropyl *syn*-aldol with phenylethylamine and subsequent treatment of the amide product with samarium(II) iodide, initiated a β-elimination reaction to afford an α,β-unsaturated amide which was reduced to Grenadamide.



Scheme 4

Finally, electrophilic cleavage of the cyclopropane motif of these *syn*-aldol substrates was explored *via* treatment of these compounds with mercury(II) trifluoroacetate for the synthesis of chiral lactones and pyrans.

Abbreviations

Ac	Acetyl
acac	Acetylacetonate
AIBN	2,2'-Azobisisobutyronitrile
aq.	Aqueous
atm	Atmosphere
9BBN	9-Borabicyclo[3.3.1]nonane
BINAP	2,2'-Bis(diphenylphospino)-1,1'-binaphthyl
BINOL	1,1-Binaphthyl alcohol
Boc	*tert*-Butyloxycarbonyl
BOP	*o*-Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluoro phosphate
Bn	Benzyl
Bu	Butyl
°C	Degrees Celsius
cat.	Catalytic
$C{=}O_{ox}$	Oxazolidin-2-one carbonyl
COD	Cyclooctadiene
Conv.	Conversion
COSY	Correlation Spectroscopy
CI	Chemical Ionisation
d	Doublet
δ	NMR Chemical Shift
δH	^{1}H-NMR Chemical Shift
δC	^{13}C-NMR Chemical Shift
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane

de	Diastereomeric Excess
DET	Diethyl Tartrate
DIBAL-H	Diisobutylaluminium Hydride
Diglyme	Diethylene glycol methyl ether
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
ee	Enantiomeric Excess
EI	Electron Ionisation
eq.	Equivalents
ES	Electrospray
Et	Ethyl
EtOH	Ethanol
Ether	Diethyl Ether
Exper.	Experimental
g	Grams
HMDS	Hexamethyldisilazide
HMPA	Hexamethylphosphorictriamide
HPLC	High Performance Liquid Chromatography
Ipc	Isopinocampheyl
^{i}Pr	Isopropyl
IR	Infrared
J	Coupling Constant
LDA	Lithium Diispropylamide
Lindlar's Catalyst	Pd on $CaCO_3$/PbO
Lit.	Literature
m	multiplet
m	*meta*
M	Molar
M^+	Molecular Ion
mb	millibar
Me	Methyl

MeOH	Methanol
mg	Milligrams
m.p.	Melting Point
MS	Molecular Sieves
m/z	Mass/Charge Ratio
NBD	Norbornadiene
NOE	Nuclear Overhauser Effect
^{n}Bu	*n*-Butyl
n-Bu	*n*-Butyl
ND	Not Determined
NMM	*N*-Methylmorpholine
NMR	Nuclear Magnetic Resonance
NR	No Reaction
o	*Ortho*
o-DPPFA	*ortho*-(diphenylphosphanyl)ferrocenylcarbonyl
p	*Para*
p-TSA	*Para*-Toluenesufonic acid
PE	Petroleum Ether
Ph	Phenyl
ppm	Parts Per Million
psi	Pounds Per Square Inch
py-BOP	*o*-Benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate
q	quartet
rel.	Relative
RT	Room Temperature
s	Singlet
t	Triplet
^{t}Bu	*tert*-Butyl
Temp.	Temperature
Tf	Triflate

TfOH	Triflic Acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

Contents

1 Introduction

Chapter 1.1 Asymmetric synthesis

1.1.1 Chiral drugs

The field of asymmetric synthesis is vital to the development of new pharmaceuticals. In 2002, chiral drugs represented a $159 billion market, with approximately 30% of all drugs currently being sold as single enantiomers.[1] Chirality arises in a molecule whose three-dimensional structure has a non-superimposible mirror image. The two mirror images of the same molecule have identical physical and chemical properties in achiral environments; however, they can exhibit distinctly different properties when interacting with chiral environments, such as receptors or enzymes within the body. Therefore, the two enantiomers of a drug can have dramatically different effects. For example, the widely used anti-inflammatory drug ibuprofen (**Figure 1.1-1**), which is produced by the chemical industry on a huge scale every year, is sold as a racemic mixture of the two enantiomers, despite most of its pharmacological activity being attributed to its (*S*)-enantiomer.[2]

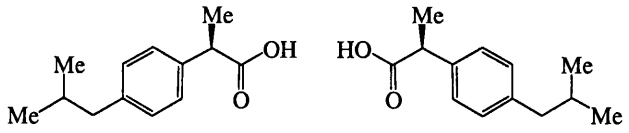
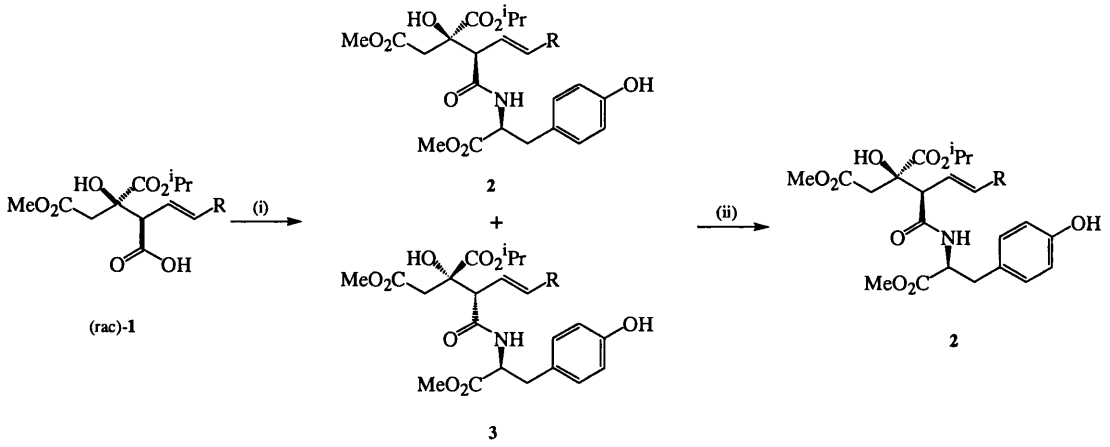


Figure 1.1-1 – *The two enantiomers of Ibuprofen*

An efficient asymmetric synthesis of the (*S*)-enantiomer would allow for a more effective drug with lower doses, whilst also creating an opportunity to extend patent protection. Therefore, the field of asymmetric synthesis continuously strives to develop new methodologies and reactions for the development of structurally challenging chiral molecules.

1.1.2 Different strategies for asymmetric synthesis

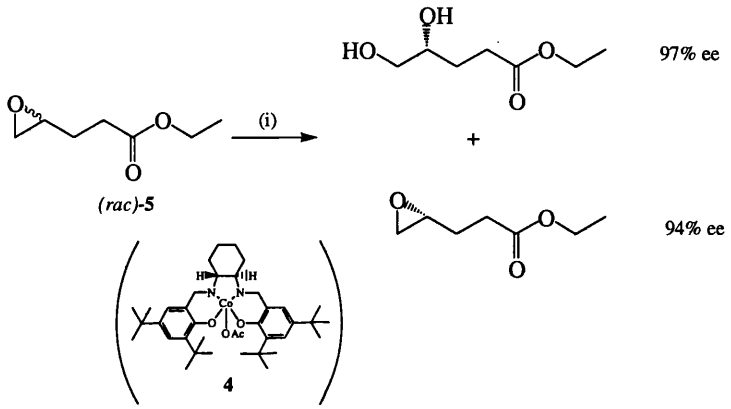
The aim of asymmetric synthesis is to construct chiral molecules in the most efficient and effective manner possible. This is a challenging task, since enantiomers display identical physical properties, other than their ability to interact with plane polarised light. The simplest way to prepare an enantiopure compound is to use a chiral building block available from nature *via* the chiral pool. These naturally occurring chiral molecules are often cheap and readily available from commercial sources and may be derivatised in a variety of ways for the synthesis of more complicated drug-like compounds. For example, Abraham and co-workers[3] have exploited L-tyrosine methyl ester for amide bond formation from acid **1**, followed by preparative HPLC separation of the resulting diastereomeric mixture (**2** and **3**) for their synthesis of the soil fungi metabolite *Veridiofungin* (**Scheme 1.1-1**).



Reagents and conditions: (i) PyBOP, NMM, CH_2Cl_2, RT; (ii) Preparative HPLC separation.

Scheme 1.1-1 – *Chiral pool synthesis from enantiopure α-amino acids*

Unfortunately, the variety of enantiopure starting materials that nature can provide is limited, as is the number of transformations that can be applied to functionalising these molecules. In order to synthesise compounds that nature does not provide easy access to it is necessary to devise alternative strategies for their asymmetric synthesis. A simple approach involves carrying out standard synthetic reactions to generate a target compound as a racemic mixture that can then be separated by kinetic resolution. For example, Liu and co-workers[4] have employed a chiral *salen* derived cobalt species **4** to catalyse stereoselective ring-opening of one enantiomer of racemic epoxide **5** in high ee for their synthesis of chiral *gamma*-lactones (**Scheme 1.1-2**).

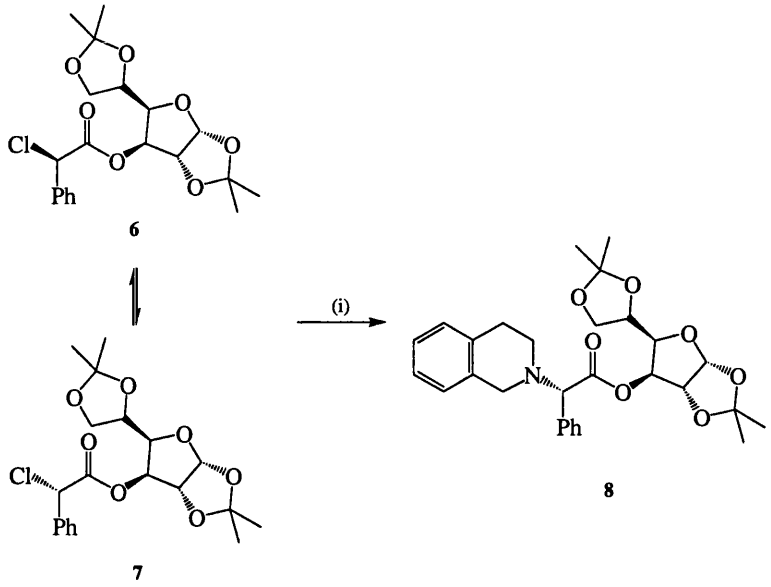


Reagents and conditions: (i) 4 (1 mol%), H_2O.

Scheme 1.1-2 – *Kinetic resolution of racemic epoxides*

The chiral catalyst reacts faster with one of the epoxide enantiomers of the racemic mixture by creating diastereomeric transition states that are different in energy, which results in differing rates of enantiomer hydrolysis affording an enantiopure diol and epoxide, which can then be easily separated by standard chromatographic methods. The main disadvantage of classical kinetic resolutions is that the maximum yield of the desired enantiomer can only be 50%. Therefore, current research in this area has been directed towards developing dynamic kinetic resolution protocols, whereby the starting material is continually racemised *in-situ*, so that >50% yields of chiral products can be achieved. Kim and co-workers[5] have demonstrated this dynamic kinetic resolution strategy for racemic α-chloro esters using diacetone-*D*-glucose as a

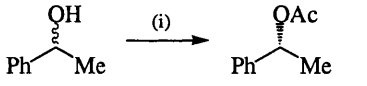
chiral auxiliary in their synthesis of chiral α-amino acids. The α-chiral centre of esters **6** and **7** are continuously epimerised under the reaction conditions, whilst the secondary amine then selectively reacts with only one of the diastereomers, to afford α-amino ester **8** in 97% yield and 94% ee (**Scheme 1.1-3**).



Reagents and conditions: (i) 1,2,3,4-Tetrahydro-isoquinoline, diisopropylethylamine, tetrabutylammonium iodide, CH_2Cl_2.

Scheme 1.1-3 – *Dynamic kinetic resolution of α-chloro esters*

Enzymes are nature's own chiral catalysts and have been exploited for asymmetric synthesis through a variety of transformations, due to the high levels of selectivity observed.[6] For example, Williams and co-workers[7] have used a lipase enzyme catalyst in the dynamic kinetic resolution of racemic alcohols. The transfer hydrogenation rhodium catalyst acted to continuously racemise alcohol **9**, so that under lipase catalysed conditions only one enantiomer of the alcohol is esterified (**Scheme 1.1-4**).



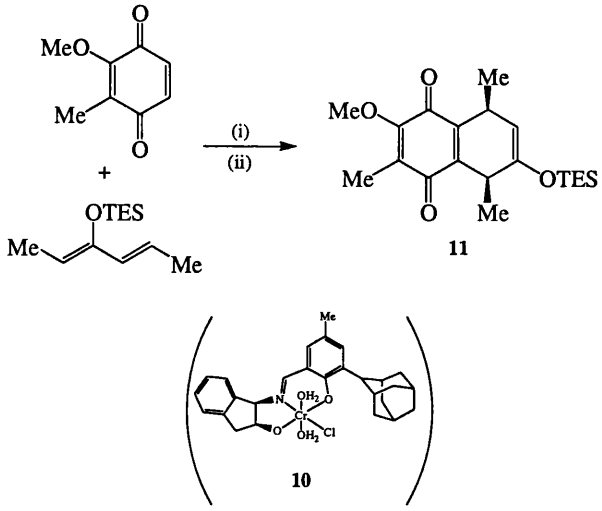
60% Conversion
98% ee

9

Reagents and conditions: (i) Pseudomonas fluorescens lipase, $Rh_2(OAc)_4$, o-phenanthroline, vinyl acetate/cyclohexane (2:1).

Scheme 1.1-4 – *Enzymatic dynamic kinetic resolution*

A potentially more efficient process is to use a chiral catalyst to prepare a chiral molecule containing *new* chiral centres. This approach again relies on the principle of diastereomeric transition states, whereby the two faces of a prochiral centre within the substrate become diastereotopic due to coordination to the chiral catalyst. For example, Jacobsen and co-workers[8] have developed a chiral chromium(III) Schiff base complex **10**, for their asymmetric Diels-Alder synthesis of quinone derivative **11**, which acts as a Lewis acid that coordinates to the quinone carbonyl to introduce stereocontrol (**Scheme 1.1-5**).

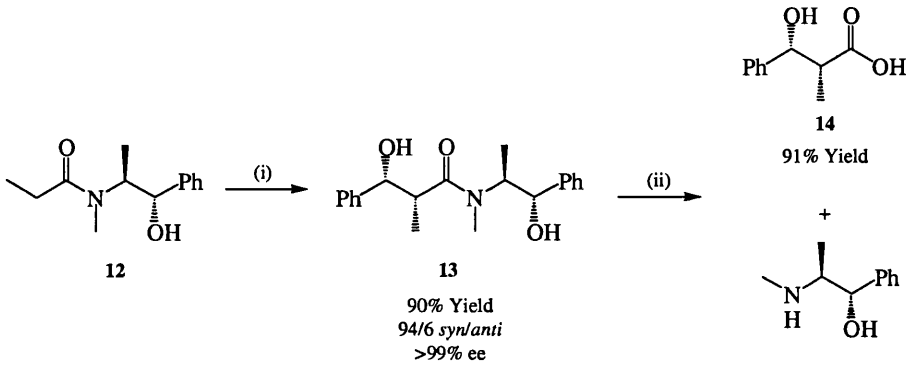


*Reagents and conditions: (i) **10** (5 mol%), toluene, 5Å MS; (ii) DBU, air.*

Scheme 1.1-5 – *Asymmetric catalysis*

Finally, the most commonly employed method for asymmetric synthesis is the use of a chiral auxiliary fragment for asymmetric induction.[9] In this approach, an

enantiopure substrate is attached to a prochiral molecule, which then controls a diastereoselective transformation before cleavage of the auxiliary for subsequent recycling. Badia and co-workers[10] have used this concept in the asymmetric synthesis of aldol substrates using (*S*,*S*)-pseudoephedrine as a chiral auxiliary. The *N*-acylated chiral auxiliary **12** underwent a zirconium mediated aldol reaction to afford aldol **13** in 90% yield, 88% de and >99% ee. It was proposed that coordination of the chiral auxiliary fragment to the zirconium catalyst was the driving force in controlling the stereoselectivity of this reaction. The chiral β-hydroxy carboxylic acid **14** was then cleaved from the chiral auxiliary fragment under acidic hydrolysis conditions in 91% yield (**Scheme 1.1-6**).



Reagents and conditions: (i) LDA, THF, then $ZrCp_2Cl_2$, then PhCHO; (ii) 4M H_2SO_4/dioxane reflux.

Scheme 1.1-6 – *Chiral auxiliaries in the asymmetric aldol reaction*

This project seeks to exploit chiral auxiliaries in a novel manner for the asymmetric synthesis of chiral aldehydes and as a consequence, a brief overview of the methods currently employed for their preparation are now discussed.

Chapter 1.2 Strategies for the asymmetric synthesis of chiral aldehydes

1.2.1 Introduction

The increasing demand for the synthesis of complex natural products and chiral drug like molecules has driven many research groups to investigate new strategies for the synthesis of versatile chiral building blocks that can be subjected to a variety of transformations. Chiral aldehydes are important compounds in this respect, due to the range of versatile reactions that the aldehyde functionality can undergo. Simple one-step transformations can convert this functional group to a variety of substrates in high yield, thereby providing a simple approach to introducing remote chirality into structurally complex molecules (**Figure 1.2-1**).[11]

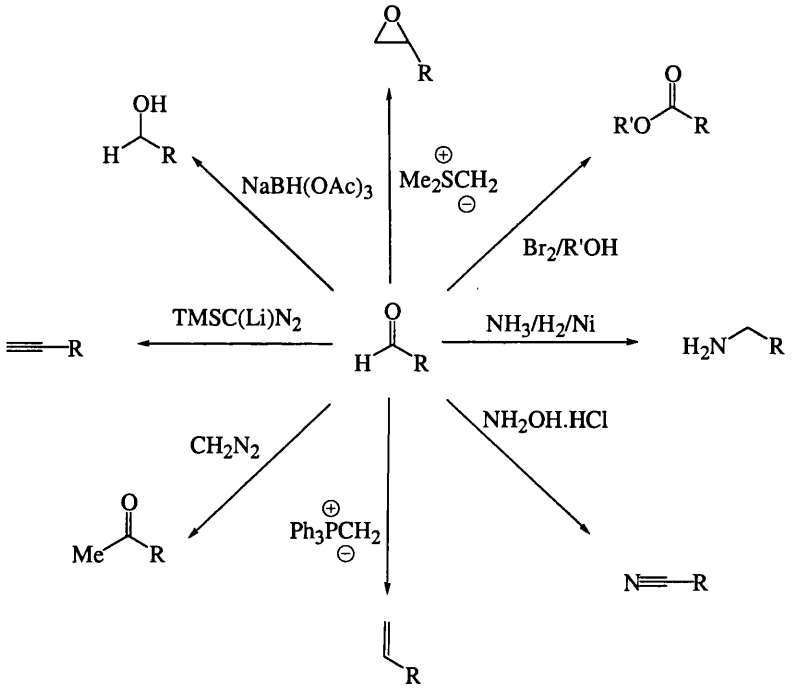
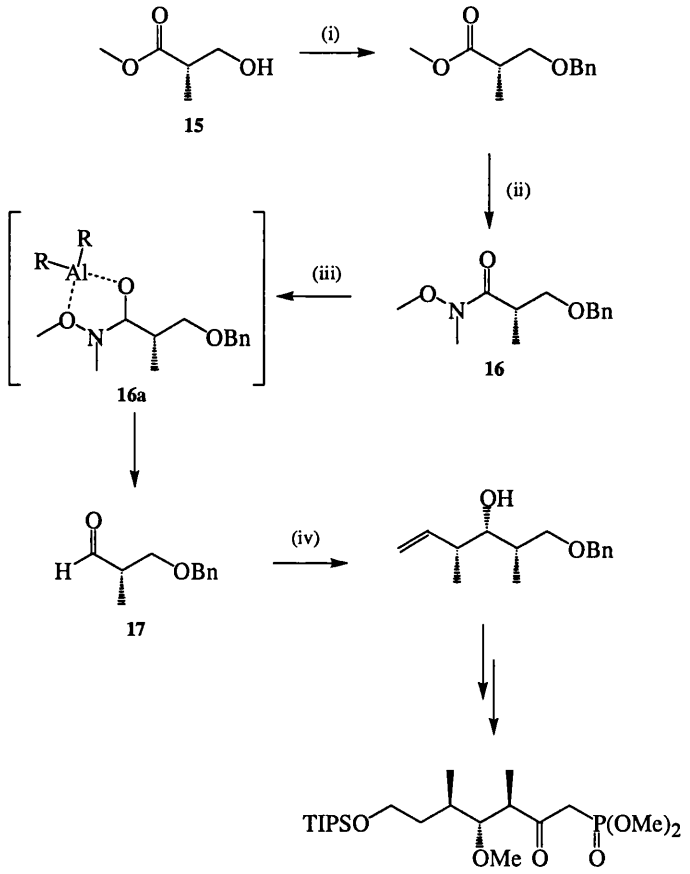


Figure 1.2-1 – *Range of one-step transformations of the aldehyde functionality*

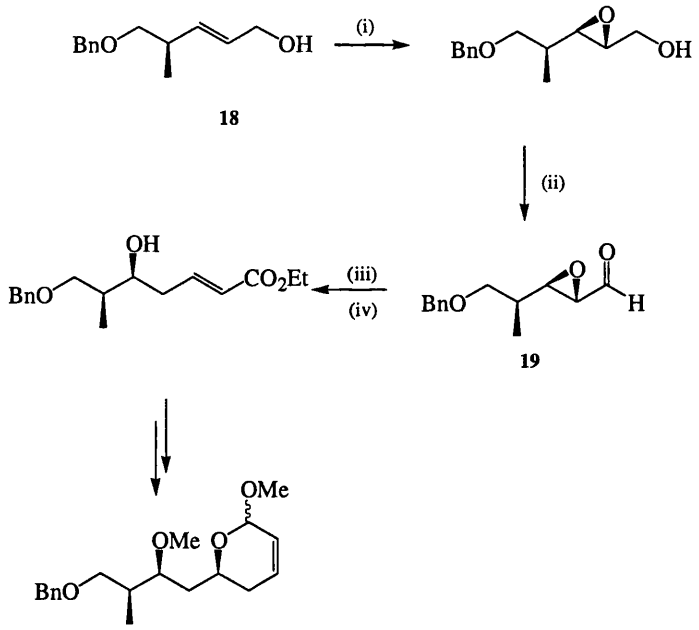
Chiral aldehydes may be synthesised from chiral amides and esters *via* hydride reduction; however, the efficiency of this reaction is often compromised by the difficulty in controlling the reactivity of the resultant aldehyde equivalent to avoid over reduction to the parent alcohol. For example, Paterson and co-workers[12] have utilised this reaction in their synthesis of *Scytophycin C* (**Scheme 1.2-1**). The key chiral aldehyde intermediate **17** was synthesised in three steps from commercially available chiral ester **15** *via* formation of Weinreb amide **16**. Coordination of the oxygen atom of the Weinreb amide motif to the counterion of the DIBAL-H reducing reagent afforded chelated intermediate **16a**, which limits over reduction to the primary alcohol in this case.



Reagents and conditions: (i) $BnOC(CCl_3)=NH$, TfOH (cat.), Et_2O; (ii) MeNHOMe.HCl, $^{i}PrMgCl$, THF; (iii) DIBAL-H, THF; (iv) (E)-butene, $KO^{t}Bu$, $^{n}BuLi$, then, (+)-Ipc_2BOMe, $BF_3.OEt_2$, then NaOH, 30% H_2O_2.

Scheme 1.2-1 – *Reductive synthesis of chiral aldehydes*

Chiral aldehydes can also be synthesised through the oxidation of primary alcohols. Miyashita and Hayakawa[13] utilised this reaction in their synthesis of a chiral fragment directed towards the asymmetric synthesis of *Swinholide* (**Scheme 1.2-2**). Therefore, Sharpless epoxidation[14] reaction of primary alcohol **18** followed by subsequent Swern oxidation afforded chiral aldehyde **19**, with no epimerisation of the potentially labile α-stereocentre. The mechanism of the Swern oxidation reaction prevents any over oxidation to corresponding carboxylic acid.[15]



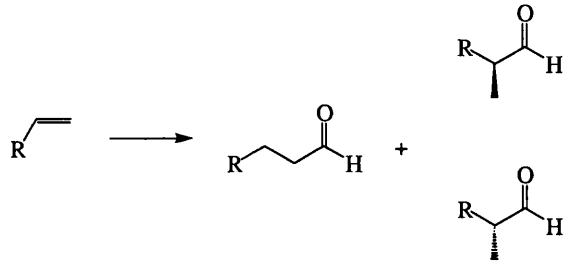
Reagents and conditions: (i) $Ti(O^iPr)_4$, D-(-)-DET, ^tBuOOH, CH_2Cl_2; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N; (iii) $Na[PhSeB(OEt)_3]$, AcOH, EtOH; (iv) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF.

Scheme 1.2-2 – *Oxidative synthesis of chiral aldehydes*

These two strategies rely on manipulation of the oxidation state of the parent chiral substrate molecule, which clearly increases the number of steps in the synthetic protocol and risks epimerisation of any newly formed stereocentres. Therefore, this review will now focus on methodologies for the direct asymmetric synthesis of chiral aldehydes that do not rely on oxidative/reductive steps to generate the aldehyde functionality.

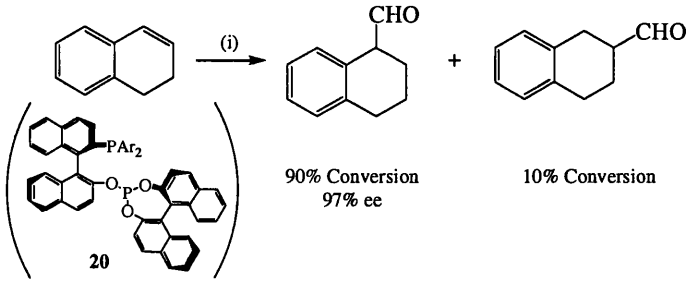
1.2.2 Asymmetric hydroformylation

Hydroformylation is an atom efficient one-carbon homologation reaction for converting an alkene functionality into an aldehyde. The key challenge in this reaction is the formation of the new carbon-carbon bond with both high regio- and enantioselectivity (**Scheme 1.2-3**).[16]



Scheme 1.2-3 – *Potential products arising from the hydroformylation of mono-substituted alkenes*

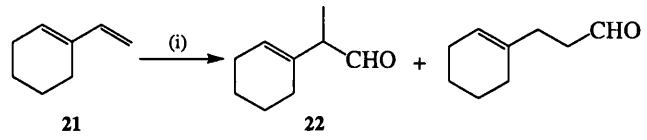
Takaya and co-workers[17] have developed a protocol for the asymmetric hydroformylation of olefins catalysed by a chiral phosphinephosphite-rhodium(I) complex derived from ligand **20**. The reaction was shown to be effective for the hydroformylation of various acyclic and cyclic 1,2-disubstituted olefins (**Scheme 1.2-4**) with up to 97% enantioselectivity and 90% regioselectivity. Unfortunately, the reaction requires high pressures of hydrogen and carbon monoxide gas to obtain these high levels of conversion.



*Reagents and conditions: (i) $Rh(acac)(CO)_2$ (cat.), **20**, H_2/CO (1/1, 100 atm), benzene. Note; absolute configuration of products not determined.*

Scheme 1.2-4 – *Rhodium(I) catalysed asymmetric hydroformylation of 1,2-disubstituted olefins*

This protocol was further expanded for the asymmetric hydroformylation of conjugated dienes once again using the chiral phosphinephosphite rhodium(I) complex catalyst derived from ligand **20** (**Scheme 1.2-5**).[18] The reaction proved to be highly selective for the terminal alkene functionality of diene **21**, affording chiral β-γ-unsaturated aldehyde **22** with 7.3:1 regioselectivity and 96% enantiomeric excess respectively.



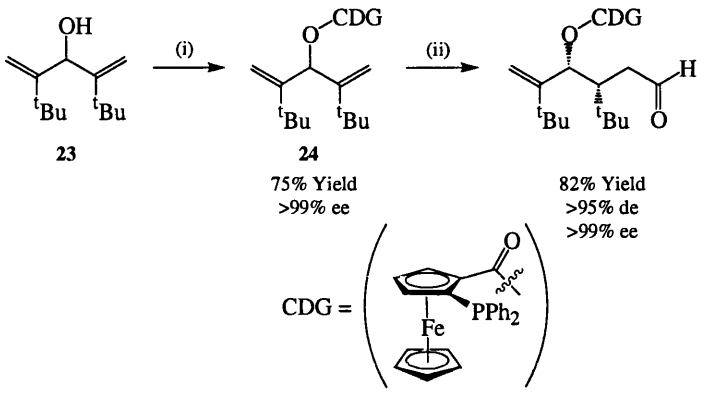
21 **22**

78% conversion
7.3:1 regioselectivity
96% ee

Reagents and conditions: (i) $Rh(acac)(CO)_2$ (cat.), 20, H_2/CO (1/1, 100 atm), benzene. Note, absolute configuration of products not determined.

Scheme 1.2-5 – *Asymmetric hydroformylations of conjugated dienes*

Due to limitations with this phosphite ligand strategy, Breit and co-workers[19] developed a substrate-bound catalyst directing group strategy for the asymmetric hydroformylation of prochiral *bis*-alkenyl carbinols. The desymmetrisation of these compounds is achieved through the formation of an *o*-diphenylphosphanyl ferrocene adduct **24,** *via* coordination of the hydroxyl oxygen atom of *bis*-alkenyl carbinol **23**. This catalytic species then directs the hydroformylation reaction to one of the alkene functional groups with excellent enantio- and diastereoselectivity (**Scheme 1.2-6**). Cleavage of the ferrocenyl directing group was achieved through saponification; however, this did require prior protection of the aldehyde functionality as an acetonide group.

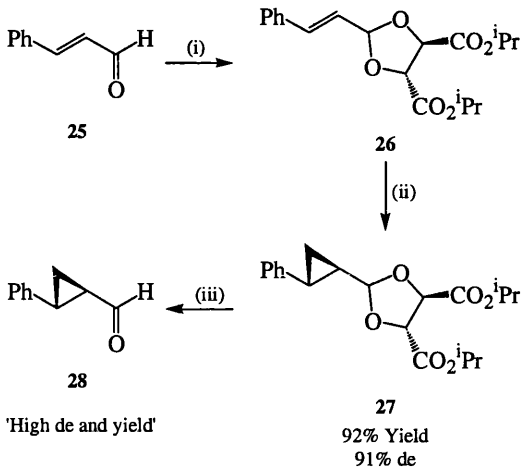


Reagents and conditions: (i) ^{t}BuLi, o-DPPFA, BOP; (ii) $Rh(CO)_2(acac)$ (cat.), $P(OPh)_3$, H_2/CO (40 bar, 1/1).

Scheme 1.2-6 – *Hydroformylation desymmetrisation*

1.2.3 Chiral auxiliaries in the synthesis of chiral aldehydes

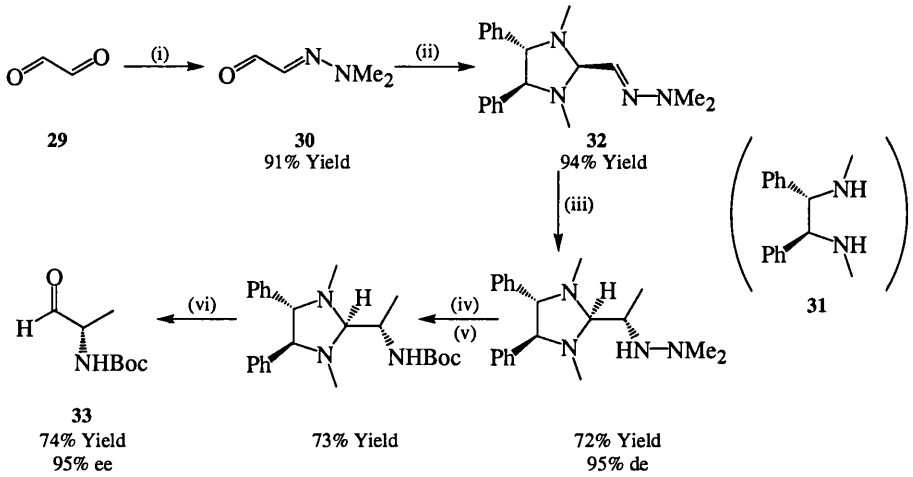
The aldehyde functionality has the potential to reversibly react with a variety of chiral molecules to afford intermediates containing prochiral fragments that may be transformed in a diastereoselective manner, before subsequent regeneration of the aldehyde functionality. For example, Yamamoto and co-workers[20] have used enantiopure tartaric acid to transform α,β-unsaturated aldehyde **25** into enantiopure acetal **26**. This substrate was then employed in a Simmons-Smith cyclopropanation reaction to afford cyclopropane acetal **27** in reasonable yield and high diastereomeric excess, which was then subsequently hydrolysed back to the cyclopropane carboxaldehyde **28** in excellent de (**Scheme 1.2-7**).



Reagents and conditions: (i) (R,R) Diisopropyl tartrate; (ii) Et_2Zn, CH_2I_2, CH_2Cl_2; (iii) p-TSA, H_2O.

Scheme 1.2-7 – *Tartaric acid directed cyclopropanation*

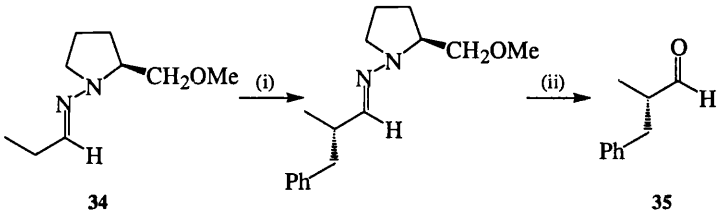
This type of aldehyde derivatisation strategy was subsequently employed by Alexakis and co-workers for converting dialdehydes into α-aminoaldehydes.[21] Glyoxal **29** was desymmetrised by formation of monohydrazone **30**, before its subsequent reaction with chiral diamine **31** to afford chiral imine **32**. The chiral imidazolidine fragment of **32** was then used to control the facial selectivity of nucleophilic attack by methyl lithium at the imine functionality, before subsequent hydrolysis to reveal the α-aminoaldehyde **33** in >95% de (**Scheme 1.2-8**).[22]



*Reagents and conditions: (i) H_2N-NMe_2, (ii) **31**, (iii) MeLi.LiBr, Et_2O; (iv) H_2, raney nickel; (v) $(Boc)_2O$; (vi) $HCl_{(aq.)}$.*

Scheme 1.2-8 – *Synthesis of chiral α-aminoaldehydes*

Enders and co-workers[23] developed this prochiral aldehyde derivatisation strategy further to generate chiral hydrazones that can act as excellent nucleophiles. Chiral hydrazone **34** was deprotonated with LDA, before subsequent alkylation with benzyl bromide. The resultant chiral hydrazone **34** was then hydrolysed to reveal the chiral aldehyde **35** in high ee (**Scheme 1.2-9**).

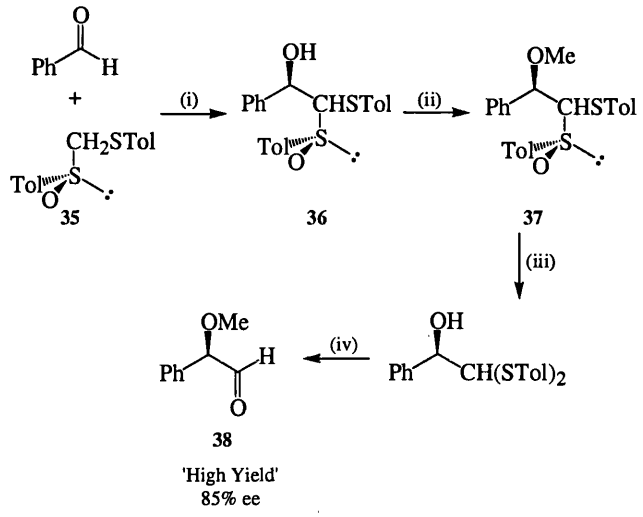


Reagents and conditions: (i) LDA, THF, -78°C to 0°C, then BnBr, -95°C; (ii) CH_3I, 60°C, then $HCl_{(aq.)}$.

Scheme 1.2-9 – *Nucleophilic chiral aldehyde derivatives*

1.2.4 Sulphur compounds as aldehyde equivalents

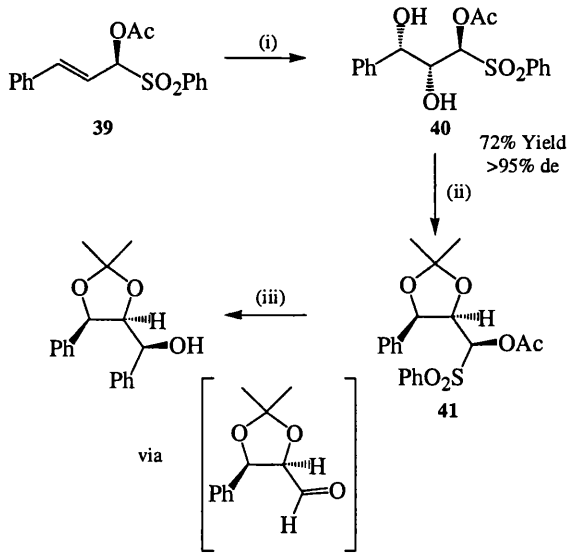
Chiral sulphur compounds can act as masked chiral aldehyde equivalents for a series of asymmetric reactions. This allows access to umpolung reactivity patterns for the aldehyde carbonyl, resulting in access to an acyl anion equivalent. Scolastico and co-workers[24] reacted the anion of chiral sulfoxide **35** with benzaldehyde to afford sulfoxide adduct **36**, which was subsequently *O*-methyl protected due to the instability of the hydroxyl intermediate to afford **37**. Reduction of the sulfoxide moiety of **37** followed by hydrolysis of the resulting dithioacetal under optimised conditions afforded chiral α-methoxyaldehyde **38** (**Scheme 1.2-10**).



Reagents and conditions: (i) $^{n}BuLi$, THF; (ii) Bu_4NOH, Me_2SO_4, H_2O, CH_2Cl_2; (iii) NaI, I_2, PPh_3; (iv) I_2, $NaHCO_3$, H_2O, dioxane.

Scheme 1.2-10 – *Sulfoxide acyl anion equivalent*

Trost and co-workers[25] further developed this strategy by derivatising α,β-unsaturated aldehydes as chiral α-acetoxysulfones. Chiral sulfone **39** was dihydroxylated with osmium tetroxide under standard conditions to afford dihydroxy sulfone **40** with excellent diastereocontrol. Attempts to hydrolyse this compound to its corresponding dihydroxy aldehyde proved unsuccessful; however, following acetonide protection of **40** to afford chiral sulfone **41**, this compound could be employed as a masked aldehyde equivalent *via* alkylation reaction with phenyl magnesium bromide (**Scheme 1.2-11**).

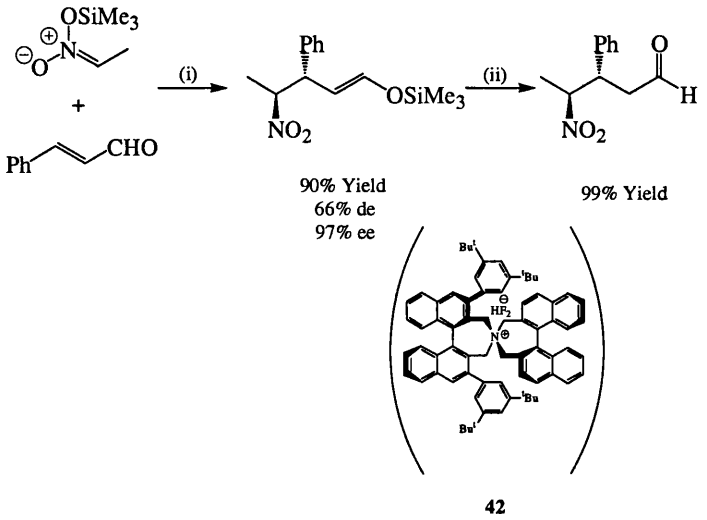


Reagents and conditions: (i) OsO_4 (cat.), NMO, CH_2Cl_2; (ii) acetone, H^+, molecular sieves; (iii) excess PhMgBr, Et_2O.

Scheme 1.2-11 – *Chiral sulfones as acyl anion equivalents*

1.2.5 Conjugate additions to α,β-unsaturated aldehydes

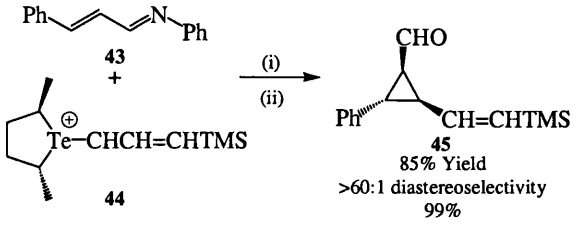
Methodology for the 1,4 addition of nucleophiles to α,β-unsaturated aldehydes presents a significant chemoselective challenge, due to the high reactivity of the aldehyde functionality towards competing 1,2-addition pathways. However, Maruoka and co-workers[26] have achieved a 32:1 chemoselective chiral 1,4-addition of silyl nitronates to α,β-unsaturated aldehydes using a chiral quaternary ammonium bifluoride catalyst **42** (**Scheme 1.2-12**).



*Reagents and conditions: (i) **42**, (cat.), toluene; (ii) HCl.*

Scheme 1.2-12 – *Chiral 1,4-addition of silyl nitronates to aldehydes*

The Michael addition/elimination reaction of ylides to electron deficient olefins is an important reaction for the synthesis of functionalised cyclopropanes. Although this protocol has been successful for the cyclopropanation of α,β-unsaturated esters[27] and amides,[28] the inherent reactivity of the aldehyde functionality makes a comparable reaction on these substrates challenging, due to potential carbonyl epoxidation. Tang and co-workers[29] solved this problem by carrying out tellurium ylide mediated cyclopropanation reactions of α,β-unsaturated imines (**Scheme 1.2-13**). For example, unsaturated imine **43** was reacted with the sodium anion of chiral tellurium ylide **44** to afford chiral cyclopropane imine that was treated with damp silica gel, which resulted in imine hydrolysis to afford chiral 1,2,3-substituted carboxaldehyde **45** with high enantio- and diastereoselectivity.

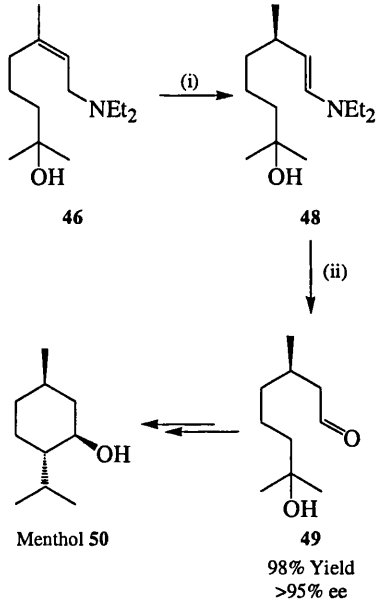


Reagents and conditions: (i) NaHMDS, HMPA, THF, -78°C; (ii) SiO_2.

Scheme 1.2-13 – *Stereoselective cyclopropanation with tellurium ylides*

1.2.6 Catalytic asymmetric isomerisation

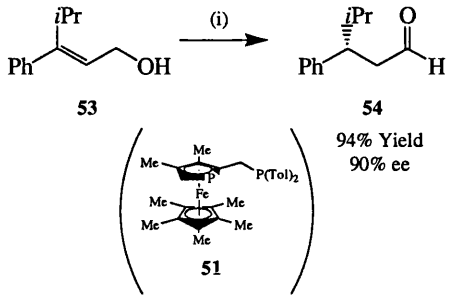
The catalytic enantioselective isomerisation of allylic amines has been proven to be a highly successful strategy for the synthesis of chiral aldehydes. Otsuka and co-workers first described this reaction in 1978[30] and this protocol has since been developed for the highly enantioselective synthesis of menthol,[31] which has now been applied on an industrial scale (**Scheme 1.2-14**).[32] It has been proposed that the reaction proceeds either through either a 1,2-hydride shift mechanism or through the formation of a π-allyl intermediate. Allylic amine **46** was treated with chiral rhodium(I) catalyst **47** to generate chiral enamine **48**, which is subsequently hydrolysed to afford the key chiral aldehyde **49** for the synthesis of menthol **50**.



Reagents and conditions: (i) [Rh((-)-BINAP)(NBD)]ClO_4 47 (cat), THF, 100°C; (ii) $H_2SO_{4(aq.)}$.

Scheme 1.2-14 – *Rhodium catalysed enantioselective isomerisation of allylic amines*

Fu and co-workers sought to adapt this reaction to a comparable enantioselective isomerisation of allylic alcohol substrates (**Scheme 1.2-15**).[33] Using chiral ferrocene derived ligand **51** to afford chiral rhodium complex **52**, they catalysed the highly enantioselective isomerisation of allylic alcohol **53** chiral aldehyde **54** in high yield.

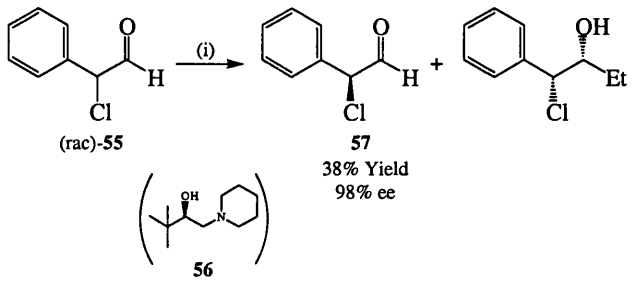


Reagents and conditions: (i) [Rh(cod)(51)]BF_4 52 (cat.), THF, 100°C.

Scheme 1.2-15 – *Enantioselective catalytic isomerisation of allylic aldehydes*

1.2.7 Kinetic resolution

Strategies for the kinetic resolution of racemic compounds are an important method for the synthesis of chiral compounds.[34] The asymmetric alkylation of aldehydes with diethyl zinc and catalytic amounts of chiral amino alcohols has proved to be a highly selective method for the synthesis chiral secondary alcohols.[35] Oguni and co-workers have exploited this reaction for the kinetic resolution of racemic aldehydes.[36] Racemic aldehyde **55** was reacted with diethyl zinc using chiral amino alcohol catalyst **56**, to leave chiral unreacted chiral aldehyde **57** with 98% enantiomeric excess. **(Scheme 1.2-16)**.



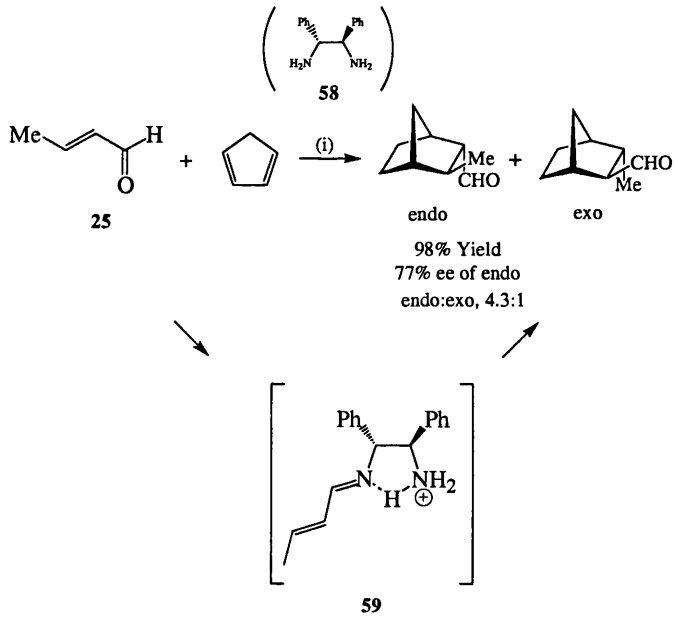
Reagents and conditions: (i) Et_2Zn, 56 (cat.), toluene.

Scheme 1.2-16 – *Kinetic resolution of racemic aldehydes*

1.2.8 Organocatalysis 1: Conjugate addition and cycloaddition reactions

The largest area of current research into the synthesis of chiral aldehydes has been in the study of organocatalytic protocols. This strategy is particularly attractive because it eliminates the need to use expensive and potentially toxic metal catalysts and the inherent problems that can arise with their removal, particularly upon scale-up.[37]

Ha and co-workers have demonstrated organocatalytic Diels-Alder reaction of α,β-unsaturated aldehyde **25** with chiral 1,2-diamino-1,2-diphenylethane catalyst **58** (**Scheme 1.2-17**).[38] It was proposed that the reaction proceeded through hydrogen bonded iminium ion intermediate **59**, which serves to control the enantioselectivity of the reaction.

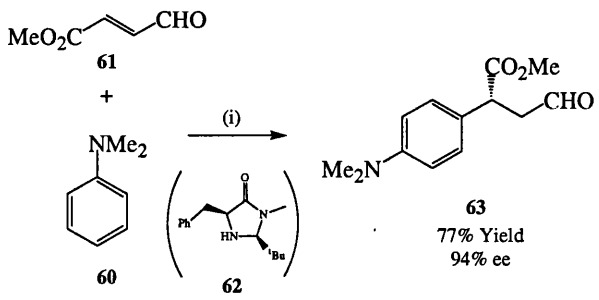


Reagents and conditions: (i) 58 (cat.), HBr, Dioxane-H_2O (95:5).

Scheme 1.2-17 – *Organocatalytic Diels-Alder reaction*

Macmillan and co-workers have previously noted that the reversible formation of iminium ions from α,β-unsaturated aldehydes lowers the energy of the olefin LUMO. Using this concept, they were able to demonstrate the conjugate addition of *N,N*-

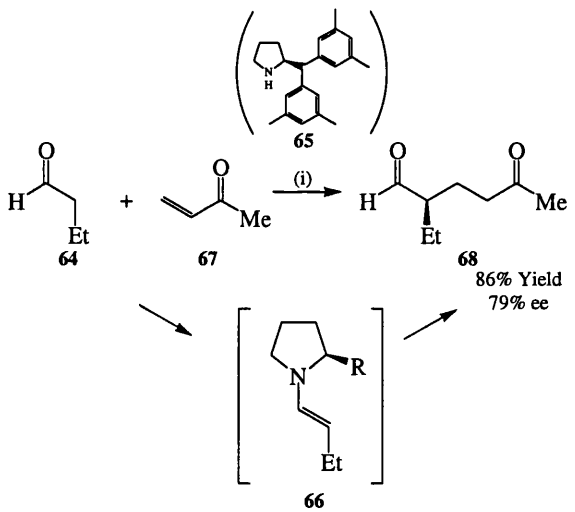
dimethyl-aniline **60** to α,β-unsaturated aldehyde **61** using a chiral imidazolidone catalyst **62**, to afford chiral benzylic aldehyde **63** with high enantioselectivity and yield (**Scheme 1.2-18**).[39]



Reagents and conditions: (i) 62 (cat.), CH_2Cl_2.

Scheme 1.2-18 – *Organocatalytic imidazolidone catalysed conjugate addition*

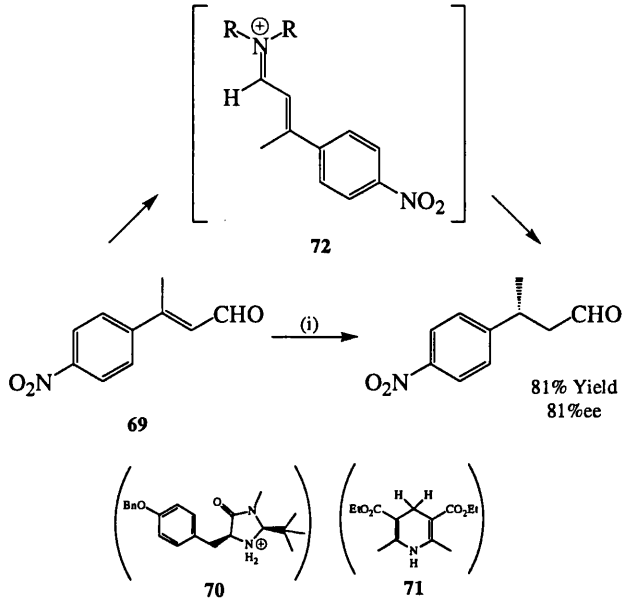
The Michael addition reaction of enolates to α,β-unsaturated carbonyl compounds is an extremely important reaction in organic synthesis. Jorgensen and co-workers have applied an organocatalytic strategy to this reaction for their synthesis of chiral 5-ketoaldehyde **68**. It was proposed that chiral amine **65** reacts *in situ* to activate aldehyde **64** as its nucleophilic enamine **66**, which then undergoes conjugate addition to methyl vinyl ketone **67** in high ee (**Scheme 1.2-19**).[40]



Reagents and conditions: (i) 65 (cat.), THF.

Scheme 1.2-19 – *Organocatalytic Michael addition*

Asymmetric hydrogenation protocols often requires expensive metal catalysts that are highly substrate specific to be effective. Preliminary work by List *et al* has recently demonstrated an asymmetric conjugate reduction reaction of α,β-unsaturated aldehyde **69** using chiral amine **70** as an organocatalyst.[41] It was proposed that Hantzch ester **71** acts as a transfer hydrogenation agent to reduce the alkene functionality of iminium ion intermediate **72** (**Scheme 1.2-20**).

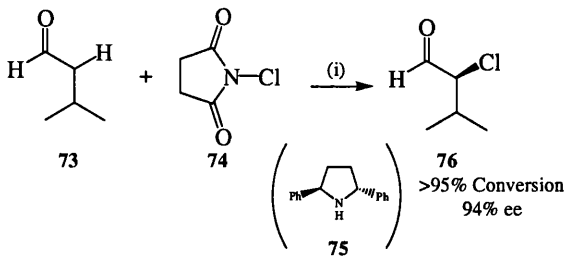


Reagents and conditions: 70 (cat.), 71 (1 equiv.), dioxane.

Scheme 1.2-20 – *Organocatalytic transfer reduction hydrogenation*

1.2.9 Organocatalysis 2: α-substitution

Heteroatom substituted chiral aldehydes are attractive building block for the synthesis of biologically active molecules, due to the versatility of synthetic methods that employ these compounds as substrates.[42] In this respect, Jorgensen and co-workers have developed an organocatalytic α-chlorination reaction of aldehydes.[43] Prochiral aldehyde **73** was treated with *N*-chlorosuccinimide **74** in the presence of chiral amine catalyst **75**, to afford α-chloroaldehyde **76** in high yield and enantioselectivity (**Scheme 1.2-21**).

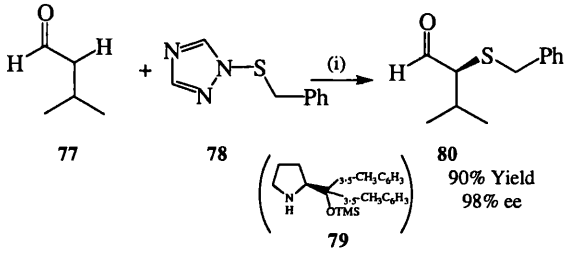


73 74 75 76

Reagents and conditions: (i) 75 (cat.), DCE, RT.

Scheme 1.2-21 – *α-Chlorination of prochiral aldehydes*

Jorgensen and co-workers subsequently expanded this protocol for the asymmetric α-sulfenylation of prochiral aldehydes.[44] Prochiral aldehyde **77** was reacted with sulfenylating reagent **78** and catalysed by chiral amine **79**, to afford α-sulfenyl chiral aldehyde **80** in 90% yield and 98% ee (**Scheme 1.2-22**).



77 78 79 80

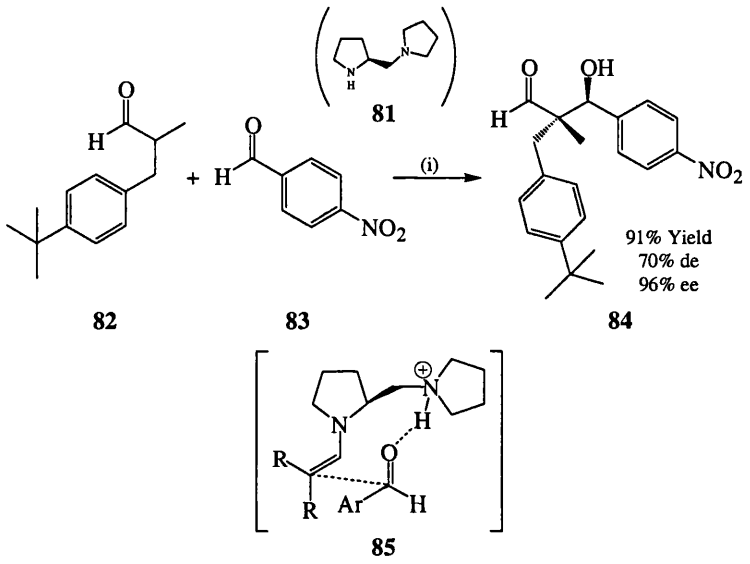
Reagents and conditions: (i) 79 (cat.), toluene.

Scheme 1.2-22 – *α-Sulphenylation of prochiral aldehydes*

1.2.10 Organocatalysis 3: Aldol reactions

Aldol reactions are some of the most widely used reactions in organic synthesis, since this carbon-carbon bond forming reaction can generate up to two new chiral centres. The cross-aldol reaction between two aldehydes presents particular difficulty, since under standard basic or acidic enolate equivalent forming conditions, the reaction invariably results in a mixture of homocoupled aldol substrates due to the inherent reactivity of the aldehyde functionality to nucleophilic addition. Tanaka and co-workers have developed an organocatalytic solution to this problem.[45] Using a chiral

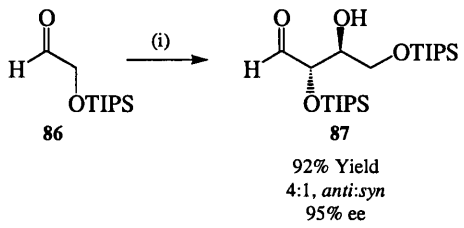
proline derived catalyst **81**, they were able to demonstrate a cross-aldol reaction between an aliphatic aldehyde **82** and an electron deficient aryl aldehyde **83** to afford aldol adduct **84** with high levels of stereocontrol, particularly considering that this reaction results in the formation of a chiral quaternary carbon centre (**Scheme 1.2-23**). It was proposed that the origin of stereoselectivity in this reaction was due to the hydrogen bonded transition state **85**, which delivers the electron deficient aldehyde to one face of the enamine intermediate.



*Reagents and conditions: (i) **81** (cat.), CF_3CO_2H (cat.), DMSO.*

Scheme 1.2-23 – *Organocatalytic cross-aldol reaction*

Similarly, Macmillan and co-workers have utilised a proline aldol strategy for their elegant asymmetric synthesis of various carbohydrate derivatives.[46] The protocol requires asymmetric dimerisation of two α-oxyaldehydes **86**, to afford aldol product **87**, which does not react further despite containing a comparable α-oxyaldehyde functionality (**Scheme 1.2-24**).



86 **87**

92% Yield
4:1, *anti:syn*
95% ee

Reagents and conditions: (i) L-proline (cat.).

Scheme 1.2-24 – *Aldehyde dimerisation*

1.2.11 Conclusion

This brief review serves to illustrate the variety of methods for the asymmetric synthesis of chiral aldehydes; however, it is reasonable to conclude that the development of methodology for the asymmetric synthesis of this class of compound remains a significant challenge.

2 Results and Discussion

Chapter 2.1 A novel strategy for using temporary stereocentres in asymmetric synthesis

2.1.1 Introduction

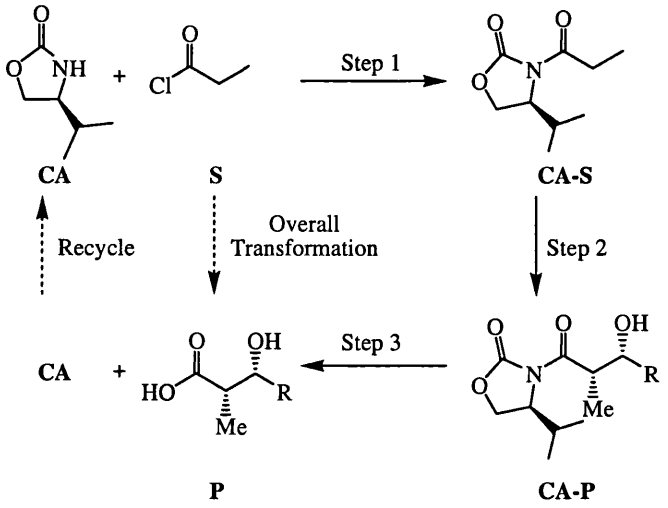
This Chapter establishes the key principles of a new three-step strategy for the asymmetric synthesis of chiral aldehydes that employs the concept of temporary stereocentres for stereocontrol. It describes how a conventional chiral auxiliary approach, normally employed for the asymmetric synthesis of enantiopure α-alkyl-β-hydroxy acids, can be modified to establish a three-step asymmetric aldol/substrate directed transformation/*retro*-aldol strategy for the stereoselective synthesis of chiral aldehydes. Previous work carried out within the SDB group towards the development of this new three-step strategy is first described. This details how methodology for highly diastereoselective *syn*-aldol reactions of racemic *N*-acylated oxazolidin-2-ones was established and describes the discovery of a novel rearrangement/elimination reaction of alkoxides of these types of *syn*-aldol substrates. My research into the application of this methodology to convert chiral *syn*-aldol substrates into their corresponding chiral 1,3-oxazinane-2,4-diones, as well as the synthesis of the (*E*)-amide functionality of the natural product *Semiplenamide C*, is then discussed. Finally, the use of a chiral SuperQuat oxazolidin-2-one auxiliary for asymmetric *syn*-aldol reactions is described, with the resultant aldols being shown to undergo the desired *retro*-aldol reactions under basic conditions.

2.1.2 A conventional chiral auxiliary approach for the asymmetric synthesis of chiral β-hydroxy acids

The versatility of the aldehyde functionality, both in terms of its reactivity and the range of transformations it undergoes, has made this class of substrate a highly desirable building block for organic synthesis. A wide range of simple one step conversions of chiral aldehydes to a variety of other functional groups are known,[11] which contributes greatly to their widespread popularity as substrates for the asymmetric synthesis of natural products and important biologically active molecules.[47]

As described in the introduction of this thesis, there are currently relatively few methods for the direct synthesis of chiral aldehydes that do not rely on oxidative[13] or reductive[12] protocols, with the inherent problems these redox approaches bring in terms of selectivity and reactivity. The aim of this project was to develop a novel three-step strategy to synthesise chiral aldehydes. This process would exploit the well-established stereodirecting control of chiral auxiliaries[48] to mediate a reversible aldol reaction, thus generating a temporary stereocentre that would be used to direct a diastereoselective reaction[49] on a prochiral fragment within the aldol substrate.

In the development of this protocol we chose to use chiral oxazolidin-2-ones, also known as Evans' auxiliaries, since this class of chiral auxiliary had been shown previously to afford excellent stereocontrol for a wide range of transformations. For example, a conventional three-step procedure that has been widely employed to carry out stereoselective aldol reactions for the asymmetric synthesis of chiral α-alkyl-β-hydroxy carboxylic acids is described in **Scheme 2.1-1**.[50]



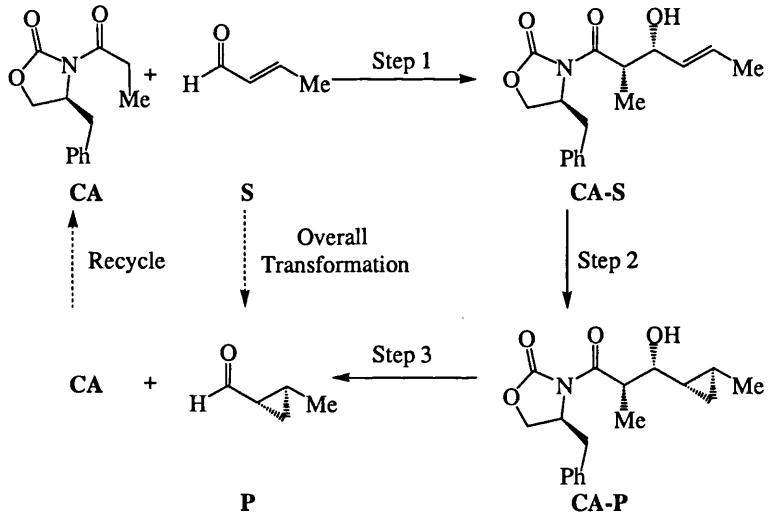
Scheme 2.1-1 – *Conventional three-step procedure for the synthesis of chiral β-hydroxy carboxylic acids*

In *step 1*, a prochiral acid derivative (**S**) is attached to the chiral auxiliary (**CA**) to generate a new chiral substrate (**CA-S**). In *step 2*, the chiral oxazolidin-2-one fragment is used to control the facial selectivity of a diastereoselective aldol reaction, generating two new chiral centres (**CA-P**). Finally, in *step 3* the substrate is cleaved, releasing the chiral auxiliary (**CA**) for recycling and the target chiral α-alkyl-β-hydroxy carboxylic acid (**P**). Overall, the three-step protocol converts a prochiral acid (**S**) into a chiral acid (**P**), containing two new stereocentres in high de. This general strategy, using oxazolidin-2-one derived chiral auxiliaries, has been shown to be effective for a wide range of transformations; including alkylations,[51] conjugate additions[52] and Diels-Alder reactions.[53]

2.1.3 A new three-step procedure for the synthesis of chiral aldehydes

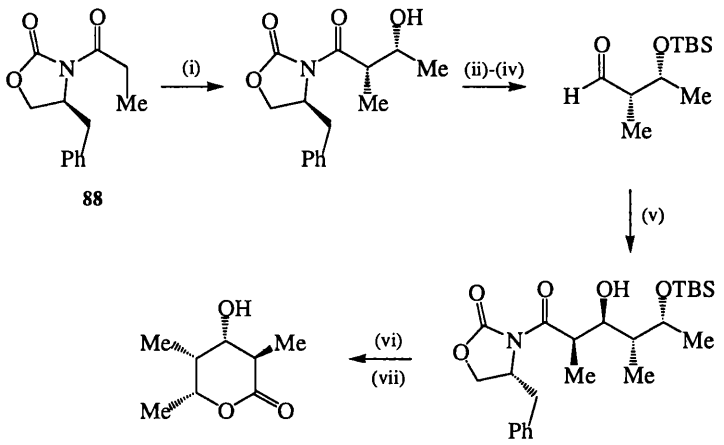
It was proposed that a new strategy could be developed using chiral oxazolidin-2-ones for the direct asymmetric synthesis of chiral aldehydes, using the novel stereoselective cyclopropanation strategy described in **Scheme 2.1-2**.

In *step 1*, the *N*-acylated oxazolidin-2-one chiral auxiliary (**CA**) would react *via* an asymmetric aldol reaction with a prochiral aldehyde (**S**), under the stereocontrol of the chiral oxazolidin-2-one fragment to generate a new chiral substrate (**CA-S**). This new chiral substrate (**CA-S**) would contain a stereodefined hydroxyl functionality, the *temporary stereogenic centre*, which would then be used in *step 2* to direct a diastereoselective transformation on the prochiral alkene fragment, to generate a second chiral substrate (**CA-P**). Finally in *step 3*, the substrate (**CA-P**) would be cleaved *via* a *retro*-aldol reaction, which destroys the *temporary stereogenic* hydroxyl functionality, thus generating a new *chiral aldehyde* (**P**). Overall, this three-step procedure would convert the prochiral α,β-unsaturated aldehyde (**S**) into chiral cyclopropane carboxaldehyde (**P**).



Scheme 2.1-2 – *New three-step procedure for the asymmetric synthesis of chiral aldehydes*

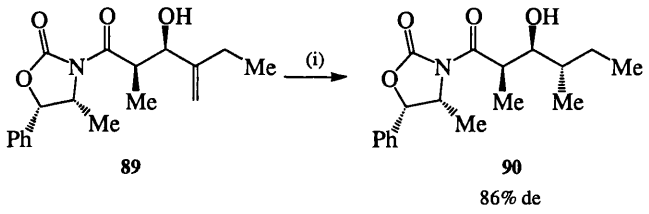
There was clear literature precedent that the new three-step strategy described in **Scheme 2.1-2** might prove successful for the asymmetric synthesis of chiral aldehydes. Firstly, *N*-acyl-oxazolidin-2-one mediated asymmetric aldol reactions have been used previously in a large number of transformations to afford either *syn*- or *anti*-aldols with high diastereoselectivity. For example, Staunton and co-workers used a phenylalanine derived oxazolidin-2-one chiral auxiliary **88** for a *syn*-aldol reaction to synthesise a polypropionate sub-unit in their total synthesis of *Erythromycin* (**Scheme 2.1-3**).[54]



Reagents and conditions: (i) Dibutyl boron triflate, Et_3N, MeCHO, CH_2Cl_2; (ii) $AlMe_3$, MeONHMe.HCl, THF; (iii) TBDMS-OTf, imidazole, DMAP, THF; (iv) DIBAL-H; CH_2Cl_2; (v) N-propionyl-oxazolidin-2-one ent-88, dibutyl boron triflate, Et_3N, CH_2Cl_2; (vi) H_2O_2, LiOH, THF/H_2O; (vii) HCl, THF/H_2O.

Scheme 2.1-3 – *An asymmetric syn-aldol reaction used for the synthesis of Erythromycin*

Additionally, for the case of substrate directable transformations, Evans and co-workers had shown that the hydroxyl functionality of *syn*-aldol product **89** could be used to carry out a directed hydrogenation reaction on its alkene group, affording **90** containing a new stereogenic centre with high diastereocontrol (**Scheme 2.1-4**).[55]

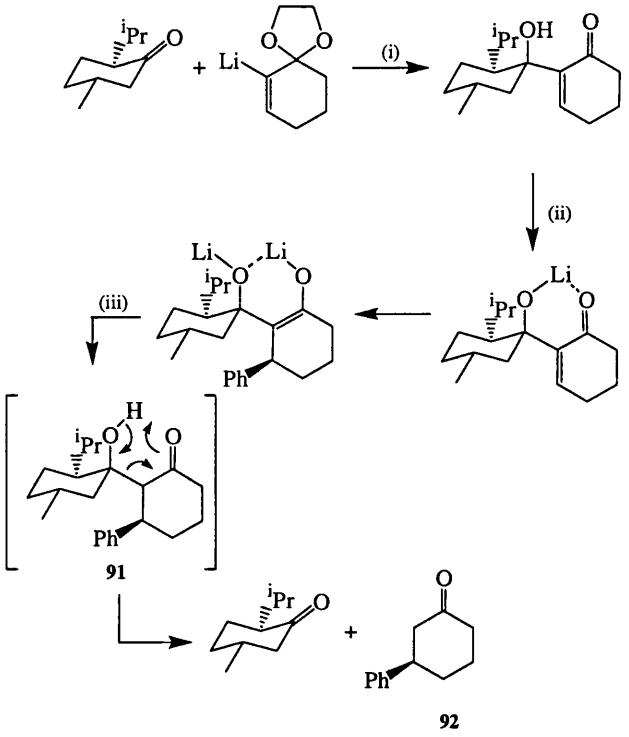


Reagents and conditions: (i) H_2 (640 psi), $[Rh(NBD)DIPHOS\text{-}4)]BF_4$.

Scheme 2.1-4 – *Directed hydrogenation reaction of a syn-aldol substrate*

Finally, while the *retro*-aldol reaction has often been observed as an unwanted side reaction in total synthesis,[56] or has been used for the degradation of natural products,[57] Funk and Yang have previously employed this reaction for asymmetric synthesis. They were able to exploit this reaction in a one-pot conjugate addition protocol for the asymmetric synthesis of β-aryl-ketone **92**, where the chiral auxiliary

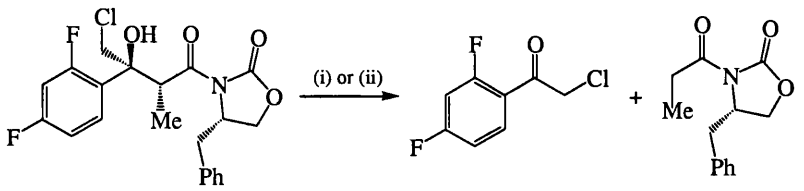
fragment of aldol **91** was removed in the final step *via* a *retro*-aldol reaction (**Scheme 2.1-5**).[58]



Reagents and conditions: (i) Oxalic acid, CH_2Cl_2/H_2O; (ii) $Ph_2CuCNLi_2$; (iii) MeOH

Scheme 2.1-5 – *The retro-aldol reaction of menthol derived β-hydroxy ketones*

Whilst there were no previous examples of *retro*-aldol reactions having been reported for *N*-acyl-oxazolidin-2-one *syn*-aldols, Bartroli and co-workers had described an unwanted *retro*-ketol reaction for related substrates in their synthesis of antifungal agents.[59] In an attempt to form an epoxide, they found that treatment of ketol **93** with LiHMDS and NaHMDS in THF at -20°C and -40°C respectively, initiated a clean *retro*-ketol reaction to afford α-chloroketone **94** and *N*-acyl-oxazolidin-2-one **88** (**Scheme 2.1-6**).



93 **94** **88**

Reagents and condition; (i) LiHMDS, THF, -78°C to -20°C; (ii) NaHMDS, THF, -78°C to -40°C.

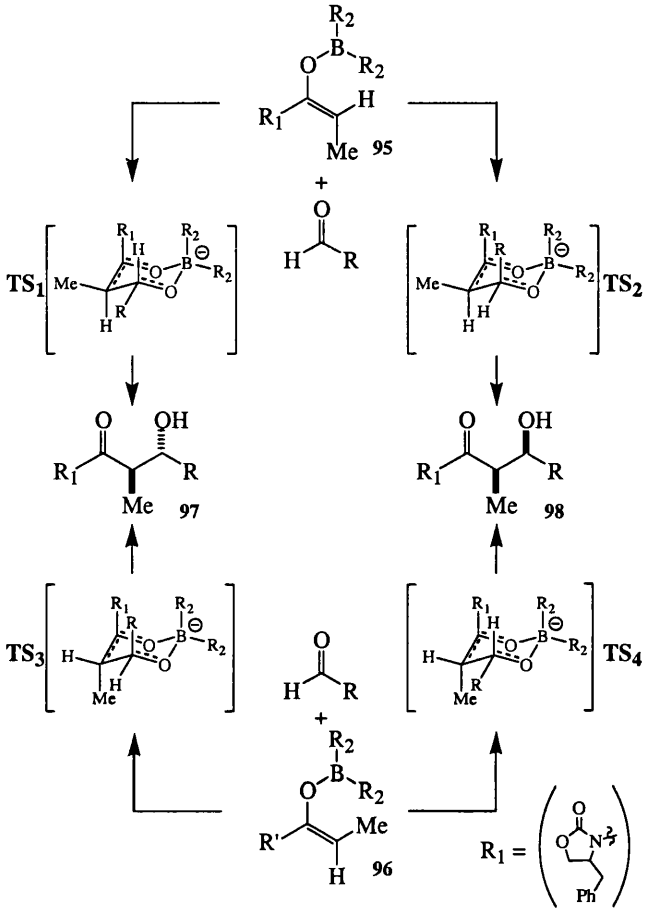
Scheme 2.1-6 – *Metal alkoxide mediated retro-ketol reaction*

In order for our proposed three-step aldol/directed transformation/*retro*-aldol protocol to become a useful addition to synthetic methodology, each of the three reactions employed would have to be high yielding and show high levels of stereocontrol. If successful, the variety of substrate directable transformations described in the literature would then allow for a wide range of chemical diversity to be introduced into the chiral aldehyde substrates using this methodology. This synthetic flexibility would outweigh any disadvantage associated with using a chiral auxiliary strategy for asymmetric synthesis, since this chiral auxiliary approach would ensure high levels of stereocontrol for a wide range of substrates, whilst enabling diastereomeric intermediates to be purified to homogeneity *via* simple recrystallisation or chromatography.

2.1.4 The asymmetric aldol reaction

Previous work within the SDB group had been directed towards establishing efficient protocols for the aldol reaction of *N*-acyl-oxazolidin-2-ones, and the *retro*-aldol reaction of β-hydroxy *N*-acyl-oxazolidin-2-ones. A racemic series of aldol products was prepared using Caddick's modification of Evans' *syn*-aldol chemistry,[60] *via* reaction of boron enolates of *N*-acylated oxazolidin-2-one derivatives with a variety of aldehydes.[61] These types of boron mediated aldol reactions are known to be *syn*-selective due to minimisation of 1,3-diaxial interactions in the aldol transition state,

as explained by consideration of the Zimmerman-Traxler transition state models described in **Scheme 2.1-7**.[62]

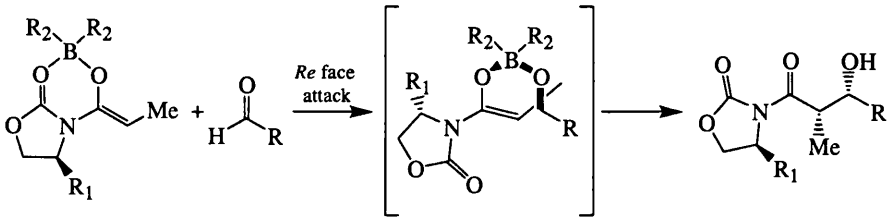


Scheme 2.1-7 – *Zimmerman-Traxler transition state model for the selectivity of aldol reactions*

The (*E*) and (*Z*) selectivity of enolate formation is vital for the stereoselectivity of these aldol reactions. When (*E*)-enolate **95** reacts with an aldehyde, two possible isomers of the six-membered transition state may occur. $\mathbf{TS_1}$ places the large R-group in an equatorial position, thus minimising 1,3-diaxial interactions in the transition state. $\mathbf{TS_2}$ places the large R-group in an axial position, maximising 1,3-diaxial interactions and as a consequence, affords a higher energy transition state when compared to $\mathbf{TS_1}$. Therefore, (*E*)-enolates generally lead to *anti*-selectivity in the aldol reaction affording *anti*-**97**. For (*Z*)-enolate **96**, the opposite selectivity occurs; for $\mathbf{TS_3}$, the bulky R-group is placed in an axial position, maximising 1,3-diaxial

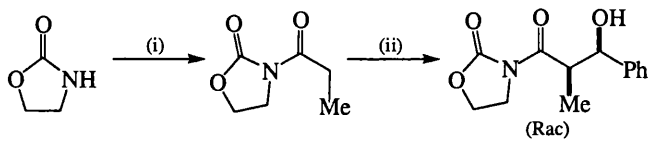
interactions and leading to a high-energy transition state. In **TS_4**, the bulky R-group is placed in the equatorial position, which affords a lower energy transition state and *syn*-selectivity in the aldol reaction to afford *syn*-aldol **98**. Boron Lewis' acid mediated enolate formation is known to afford (*Z*)-enolates with high levels of selectivity, and therefore *syn*-selectivity is normally observed in boron mediated aldol reactions.

It has been proposed that the closed transition state model described in **Scheme 2.1-8** controls the enantioselectivity of aldol reaction by coordination of the Lewis acid to the aldehyde to afford intermediate **99**,[63] in which the chiral oxazolidin-2-one fragment rotates to minimise dipole-dipole interactions, and therefore directs the aldehyde electrophile to the *Re*-face of the enolate to afford *syn*-diastereomer **100**.



Scheme 2.1-8 – *Proposed mechanism to explain the Re face attack in the oxazolidin-2-one aldol reaction*

For achiral oxazolidin-2-ones, it was shown that using 9BBN-triflate and diisopropylethylamine as base, resulted in the formation of *syn*-aldol substrates in good yield and high de **(Scheme 2.1-9)**. In a typical example, treatment of *N*-propionyl-oxazolidin-2-one **101** with 9BBN-triflate and diisopropylethylamine in dichloromethane at 0°C afforded a (*Z*)-enolate, which was reacted with benzaldehyde at -78°C before warming to 0°C, to afford (*rac*)-*syn*-aldol **102** in an acceptable 69% yield and >95% de. The relative *syn*-stereochemistry of **102** was confirmed by comparison with the previously published data for this compound, and was evident from the small coupling constant of the α-proton in the ^{1}H-NMR spectrum ($J_{2,3}$ = 3Hz), since the ^{1}H-NMR spectrum of the corresponding *anti*-diastereomer showed a larger coupling constant for its α-proton ($J_{2,3}$ = 8.5Hz).[64]



101 72% Yield

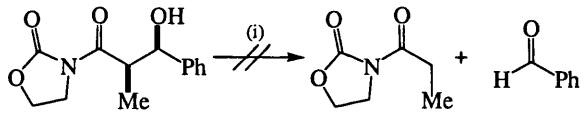
102 69% Yield >95% de

Reagents and conditions: (i) ^{n}BuLi, $CH_3CH_2CO_2Cl$, THF, -78°C, 2 hours; (ii) 9BBN-OTf, $^{i}Pr_2NEt$, 0°C, CH_2Cl_2, 1 hour, PhCHO, -78°C, 1 hour, then hold temperature at 0°C, 1 hour.

Scheme 2.1-9 – *Racemic syn-aldol reaction of achiral N-propionyl oxazolidin-2-ones*

2.1.5 An unexpected elimination reaction of racemic aldols

From the precedent of Bartoli and co-workers,[59] it was predicted that treatment of racemic *syn*-aldol product **102** with an appropriate base would initiate an anionic *retro*-aldol reaction, releasing benzaldehyde and the acylated oxazolidin-2-one chiral auxiliary **101** (**Scheme 2.1-10**).

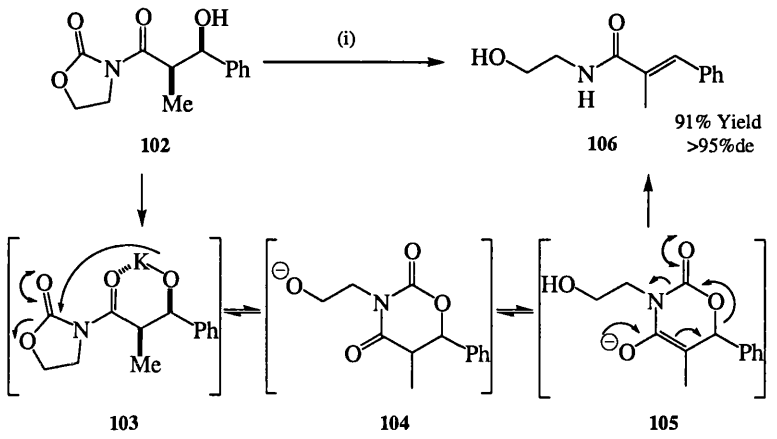


(Rac) **102** **101**

Reagents and conditions: KHMDS, THF, -78°C, 2 hours.

Scheme 2.1-10 – *Proposed anionic retro-aldol reaction*

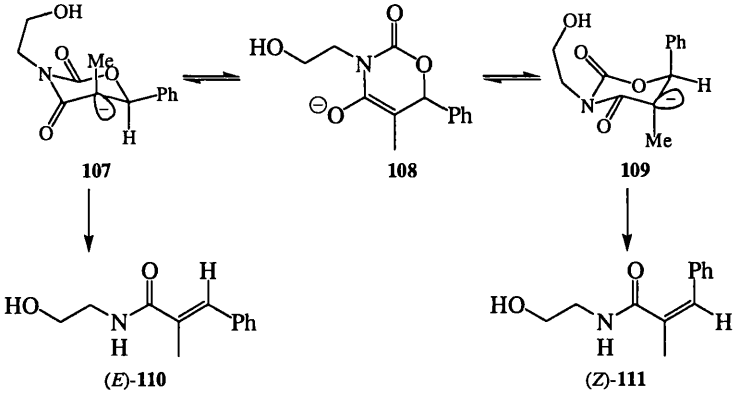
However, when this reaction was carried out no evidence of any *retro*-aldol products were observed in the crude ^{1}H-NMR spectrum; since it was found that the potassium alkoxide of **102** had instead reacted as a nucleophile, undergoing intramolecular attack at the carbonyl of the oxazolidin-2-one, followed by subsequent elimination of carbon dioxide from oxazinane-2,4-dione intermediate **104** to afford (*E*)-α,β-unsaturated amide **106** in high de (**Scheme 2.1-11**).[65]



Reagents and conditions: (i) KHMDS, THF, -78°C, 2 hours.

Scheme 2.1-11 – *Proposed mechanism for the intramolecular cyclisation/E1$_c$b type elimination of aldol products*

It was proposed that the potassium alkoxide **103** attacks the oxazolidin-2-one carbonyl in a unique intramolecular cyclisation reaction to form six-membered alkoxide intermediate **104**. Proton equilibration then affords potassium enolate **105**, which undergoes an E1$_c$b type elimination, releasing carbon dioxide, and generating the (*E*)-α,β-unsaturated amide **106** in 91% yield and >95% de. The (*E*)-selectivity of this reaction was rationalised by the simple conformational model shown in **Scheme 2.1-12**.



Scheme 2.1-12 – *Conformational model for the stereoselectivity of the E1$_c$b elimination*

There are two possible transition states that lead to either the (*E*) or (*Z*) elimination products. Transition state **107** requires overlap of the equatorial carbanion with the σ*-orbital of the C-O bond, thus allowing elimination of carbon dioxide to occur. This may only result from a chair conformer in which the methyl group occupies an axial position and the phenyl group occupies an equatorial position, resulting in the (*E*)-α,β-unsaturated amide **110**. Alternatively, the chair conformer transition state **109**, which would lead to (*Z*)-α,β-unsaturated amide **111**, would require both the methyl and phenyl groups to adopt axial positions for the same orbital overlap to occur, which is clearly higher in energy when compared to transition state **107**. This new methodology proved useful for the stereoselective synthesis of a wide range of (*E*)-α,β-unsaturated acids and (*E*)-α,β-unsaturated oxazolines (**Figure 2.1-1**).[65]

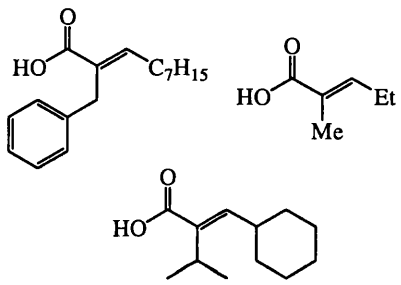
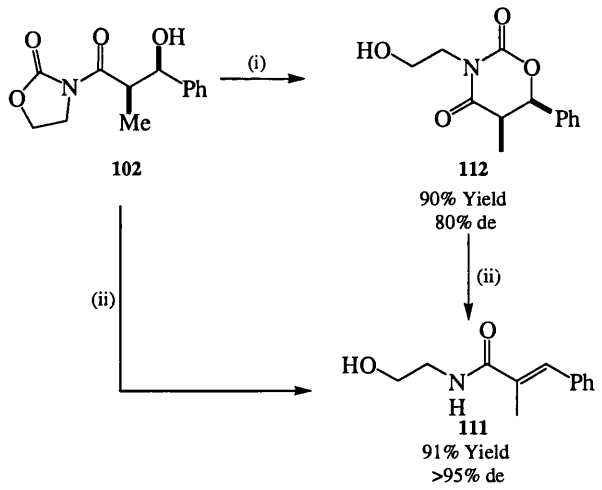


Figure 2.1-1 – *Representative examples of α,β-unsaturated acid synthesis*

2.1.6 1,4-Oxazinane-2,4-dione synthesis from racemic aldols

The mechanism of this elimination reaction was further confirmed through the synthesis of the 1,3-oxazinane-2,4-dione intermediate **108**. Softer deprotonation of *syn*-aldol substrate **102** using diethyl zinc as base, exclusively formed racemic 1,3-oxazinane-2,4-dione **112** (**Scheme 2.1-13**), without further elimination to the α,β-unsaturated amide. Subsequent treatment of racemic 1,3-oxazinane-2,4-dione **112** with KHMDS in THF at -78°C, afforded (*E*)-α,β-unsaturated amide **111**, thus demonstrating the intermediacy of **108** in this type of elimination reaction.[61]



Reagents and conditions: (i) Et_2Zn (10 mol%), CH_2Cl_2, RT, 2 hours; (ii) KHMDS, THF, -78°C, 2 hours.

Scheme 2.1-13 – *Synthesis of racemic 1,3-oxazinane-2,4-dione intermediate*

My initial goal was to explore whether *chiral N*-acyl-oxazolidin-2-ones *syn*-aldols would undergo this type of rearrangement reaction to afford either chiral 1,3-oxazinane-2,4-diones or their corresponding (*E*)-amides, since this pathway had the potential to completely derail our novel three-step strategy for the synthesis of *chiral aldehydes* described in **Scheme 2.1-2**.

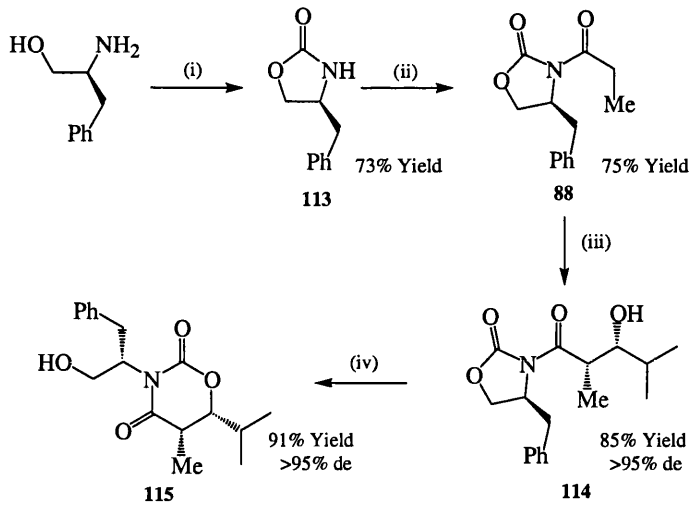
2.1.7 Development of methodology for the asymmetric synthesis of chiral 1,3-oxazinane-2,4-diones

Benzo-1,3-oxazinane-2,4-diones demonstrate a variety of biological properties[66] and have therefore been the target for development of a number of synthetic protocols.[67] Methodology for the synthesis of other types of 1,3-oxazinane-2,4-dione derivatives is less well developed, and as a consequence their biological properties are relatively poorly understood. Therefore, it was proposed that application of our aldol/diethyl zinc cyclisation protocol to chiral aldol substrates would be a useful addition to the synthesis of this class of heterocycles. The first work I carried out on this project was

to develop a chiral variant of the *syn*-aldol intramolecular cyclisation reaction to afford chiral oxazinane-2,4-diones (**Scheme 2.1-14**).

(*S*)-phenylalaninol was cyclised with diethyl carbonate as a carbonyl source under basic conditions, as adapted from Evans' standard procedure,[68] to afford (*S*)-4-benzyl-oxazolidine-2-one **113** in 73% yield. Acylation of the *N*-lithium anion of **113** in THF with propionyl chloride at -78°C afforded *N*-propionyl-(*S*)-4-benzyl-oxazolidin-2-one **88** in 75% yield. Repeating this *N*-acylation reaction, but allowing the reaction to warm from -78°C to 0°C over two hours, improved the yield of **88** to 89%. The (*Z*)-boron enolate of **88** was then generated using 9BBN-triflate as a Lewis' acid and diisopropylethylamine as base in dichloromethane at 0°C. The reaction was cooled to -78°C, isobutyraldehyde added, and the reaction stirred for one hour before being warmed to 0°C and stirred for a further hour. This gave the desired α-methyl β-isopropyl *syn*-aldol **114** ($J_{2,3}$ = 2.6 Hz) in 85% yield and >95% de.[69]

Subsequent treatment of *syn*-aldol **114** with 10 mol% of diethyl zinc caused the desired rearrangement reaction, to afford (5*S*,6*R*)-3-((*S*)-1-hydroxy-3-phenylpropan-2-yl)-6-isopropyl-5-methyl-1,3-oxazinane-2,4-dione **115** in 91% yield and >95% de. The structure of **115** was confirmed by examination of its ^{1}H-NMR spectrum, which displayed the characteristic change in chemical shift of the α-proton of *syn*-aldol **114** from δ3.96 ppm to δ2.51 ppm for the C5 proton of **115**, which arises due to the loss of anisotropic deshielding effects of the benzyl group.[70] As expected, further elimination of **115** to its corresponding α,β-unsaturated amide was not observed under these conditions.[71]

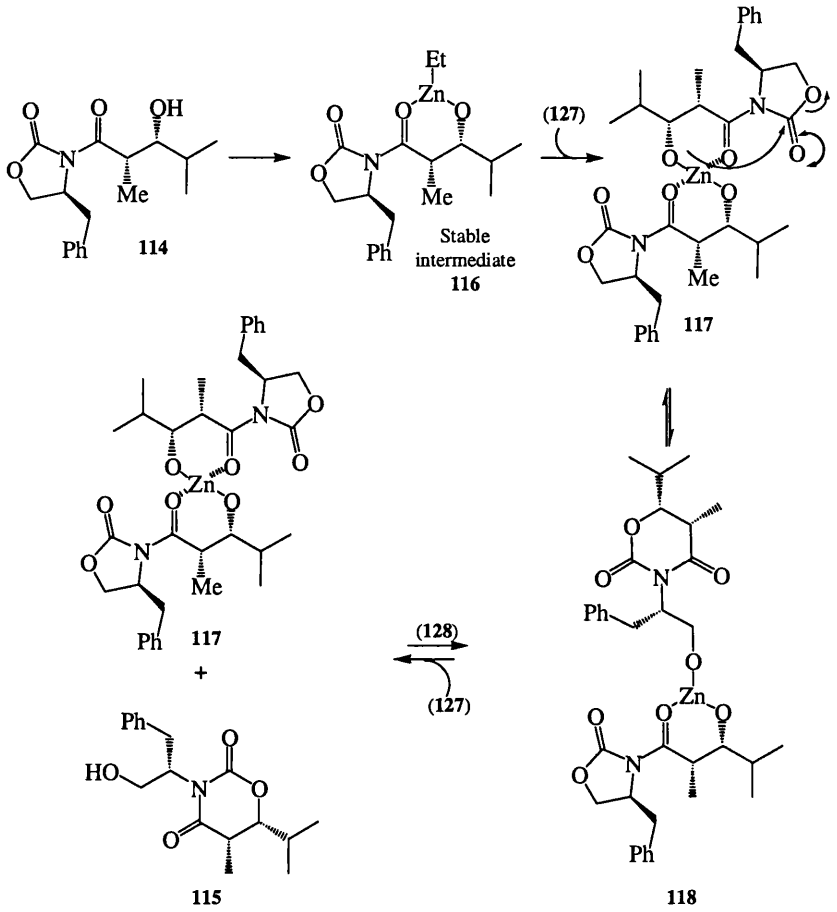


Reagents and conditions: (i) Diethyl carbonate, KO^{t}Bu, THF, 70°C, 4 hours; (ii) ^{n}BuLi, propionyl chloride, THF, -78°C to 0°C, 2 hours; (iii) 9BBN-OTf, ^{i}Pr$_2$NEt, CH_2Cl_2, 0°C, 1 hour, then isobutyraldehyde, -78°C 1 hour then 0°C 1 hour; (iv) 10 mol% diethyl zinc, CH_2Cl_2, RT, 2 hours.

Scheme 2.1-14 – *Synthesis of chiral 1,3-oxazinane-2,4-dione*

Examination of the crude ^{1}H-NMR spectrum of this rearrangement reaction revealed that approximately 10% of the *syn*-aldol **114** starting material remained. Increased reaction times had no effect on this level of conversion, indicating that this rearrangement reaction was likely to be reversible, giving a mixture of **114** and **115** products under thermodynamic control. The use of stoichiometric amounts of diethyl zinc not only failed to improve the conversion ratio, but remarkably prevented the desired rearrangement reaction from occurring.[72] Conversely, reduction in the amount of diethyl zinc to less than 10 mol% resulted in greatly increased reaction times (>6 hours).[73] In order to explain these results, it was proposed that this rearrangement reaction might be proceeding *via* a *bis*-alkoxide zinc intermediate **117** (**Scheme 2.1-15**), which activates the zinc alkoxide to nucleophilic attack at the oxazolidin-2-one carbonyl in an intramolecular fashion to afford intermediate **118**. Ligand exchange of the 1,3-oxazinane-2,4-dione fragment of **118** for another molecule of *syn*-aldol **114** could then occur to regenerate the reactive *bis*-aldol zinc intermediate **130,** which would then react further. At low concentrations of diethyl zinc (10 mol%), formation of the reactive aldol zinc dimer **117** would be favoured, which would result in the formation of oxazinane-2,4-dione **115**. Alternatively, when stoichiometric

amounts of diethyl zinc were employed as base, then formation of the stable monomeric zinc alkoxide species **116** would occur that does not undergo the intramolecular rearrangement reaction and as a consequence, the *syn*-aldol **114** is recovered.[74]



Scheme 2.1-15 – *Proposed mechanism for zinc mediated rearrangement of syn-aldols*

This methodology was subsequently employed by other members of the SDB group for the synthesis of a range of 1,3-oxazinane-2,4-diones in high yield and diastereoselectivity, representative examples of which are described in **Figure 2.1-2**.[75]

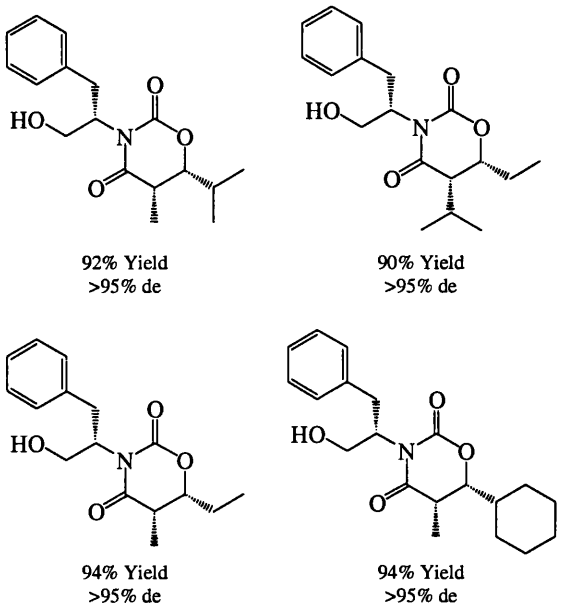


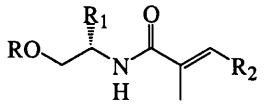
Figure 2.1-2 – *Representative examples of chiral 1,3-oxazinane-2,4-diones using our rearrangement methodology*

Having established conditions for the rearrangement of *syn*-alkoxides of chiral *syn*-aldols to their corresponding oxazinane-2,4-diones, I next decided to determine whether potassium alkoxides of chiral *syn*-aldols would eliminate further to afford their corresponding α,β-unsaturated amides. In this regard, it was decided to explore this type elimination reaction using an aldol substrate that could be used for the asymmetric synthesis of *Semiplenamide C* **119**, since this natural product represented an attractive target for this methodology.

2.1.8 Elimination reactions of *syn*-aldols for the total synthesis of *Semiplenamide C*

Semiplenamides are long chain fatty α,β-unsaturated amides, which have recently been isolated by Gerwick and co-workers from the marine cyanobacterium *Lyngbya Semiplena.*[76] These compounds have been shown to exhibit a range of biological

activity, including cytotoxicity towards a model brine shrimp system, and affinity for the rat cannabinoid receptor CB1 (**Figure 2.1-3**).[77]



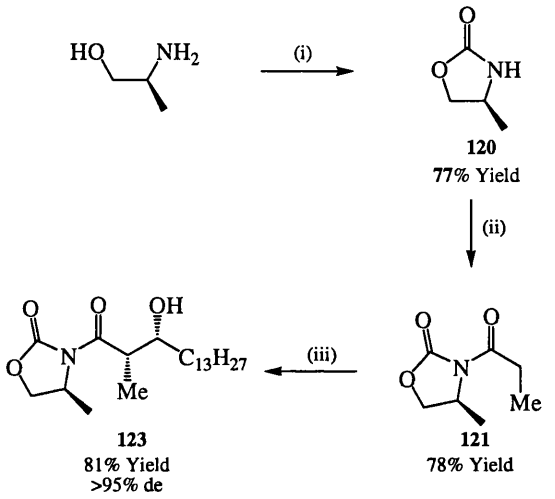
Semiplenamide A; R = H, R_1 = H, R_2 = (3*E*)-*n*-$C_{17}H_{33}$
Semiplenamide B; R = Ac, R_1 = R_2 = (3*E*)-*n*-$C_{17}H_{33}$
Semiplenamide C; R = H, R_1 = Me, R_2 = *n*-$C_{13}H_{27}$
Semiplenamide D; R = Ac, R_1 = Me, R_2 = *n*-$C_{17}H_{35}$
Semiplenamide E; R = Ac, R_1 = Me, R_2 = *n*-$C_{15}H_{31}$

Figure 2.1-3 – *Semiplenamides A-E: natural products containing α,β-unsaturated amide fragments*

In light of this biological activity and since these compounds had not been prepared previously, we were interested in synthesising *Semiplenamide C* **119** using our aldol/β-elimination methodology, which required the use of (*S*)-alaninol as a commercially available chiral starting material (**Scheme 2.1-16**).

(*S*)-Alaninol was cyclised with diethyl carbonate under basic conditions[78] to afford (*S*)-4-methyl-oxazolidin-2-one **120** in 77% yield. Acylation of the *N*-lithium anion of **120** with propionyl chloride in THF at -78°C afforded (*S*)-4-methyl-3-propionyloxazolidin-2-one **121** in 77% yield. Tetradecanal **122**, which was required for the subsequent *syn*-aldol reaction, was prepared *via* Swern oxidation of commercially available tetradecanol under standard conditions in 73% yield. The boron mediated *syn*-aldol reaction of *N*-propionyl-oxazolidin-2-one **121** and tetradecanal **122** under standard conditions (**Scheme 2.1-14**), afforded α-methyl β-tridecyl *syn*-aldol **123** in 78% yield and >95% de. The *syn*-stereochemistry of *syn*-aldol **123** was assigned from precedent discussed previously and confirmed by the small coupling constant of the α-proton ($J_{2,3}$ = 2.6 Hz). The high level of diastereoselectivity in this aldol reaction was surprising, as intuitively the decreased steric requirement of the stereodirecting methyl group of the oxazolidin-2-one fragment of **121**, when compared with *N*-propionyl-(*S*)-4-benzyl-oxazolidin-2-one **88**, might have been expected to lower the diastereoselectivity of the aldol reaction. To

the best of my knowledge this is the first example of an asymmetric aldol reaction using (*S*)-*N*-propionyl-4-methyl-oxazolidin-2-one **121** as a chiral auxiliary.[79]



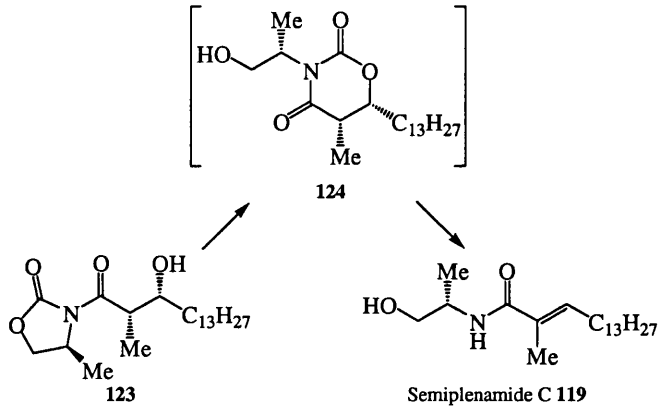
*Reagents and conditions: (i) Diethyl carbonate, KO^{t}Bu, THF, 70°C, 4 hours; (ii) ^{n}BuLi, propionyl chloride, THF, -78°C to 0°C, 2 hours; (iii) 9BBN-OTf, ^{i}Pr$_2$NEt, CH$_2$Cl$_2$, 0°C, 1 hour, then tetradecanal **122**, -78°C for 1 hour, then warm to 0°C for 1 hour.*

Scheme 2.1-16 – *Synthesis of (S)-alaninol derived syn-aldol*

With the desired *syn*-aldol substrate **123** in hand, it was then necessary to establish conditions to affect the intramolecular cyclisation/elimination reaction. There was some concern that the increased steric hindrance within the aldol substrate caused by the presence of the (*S*)-4-methyl group of the oxazolidin-2-one fragment might protect the endocyclic carbonyl from intramolecular nucleophilic attack, thus shutting down the desired elimination pathway (**Table 2.1-1**).

Treatment of *syn*-aldol **123** with KHMDS under our previously established conditions developed for the racemic aldol series (**Scheme 2.1-11, Entry 1**), resulted in a complex mixture of products being formed, which included from inspection of the crude ^{1}H-NMR spectrum the desired *Semiplenamide C* **119**.[80] It was proposed that this mixture of products had arisen from incomplete elimination of 1,3-oxazinane-2,4-dione intermediate **124**, which was revealed in the ^{1}H-NMR spectrum by the presence of a characteristic resonance for its α-proton at δ2.83 ppm.[81] I therefore undertook a screen of bases and conditions that would result in clean elimination of *syn*-aldol **123** to afford *Semiplenamide C* **119** in good yield (**Table 2.1-1**).

It was found that changing the counter-ion of the base used for deprotonation of aldol **123** from potassium to sodium (**Entry 3 and 5**) or lithium (**Entry 4**), failed to improve the conversion of the elimination reaction. It was proposed that this was likely to be due to the increased stability of chelated lithium and sodium alkoxides when compared to their potassium counterpart. Changing the base to potassium *tert*-butoxide did improve the conversion of *syn*-aldol **123** to *Semiplenamide C* **119** at -78°C (**Entry 6**), although at room temperature the formation of a third product, (*S*)-4-methyl-oxazolidin-2-one **120** was also observed (**Entry 7**). The origin of the parent oxazolidin-2-one **120** in this reaction remains undetermined; however, it is not believed to arise from a *retro*-aldol reaction, since none of the corresponding non-volatile aldehyde **122** was observed in the crude ^{1}H-NMR spectrum.[82]

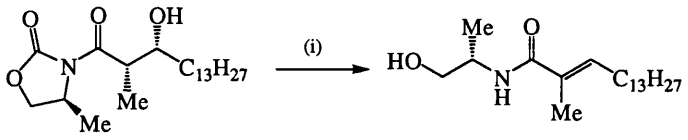


Entry	*Base*	*Solvent*	*Temp. (°C)*	*Conv. ratio* ***123:124:119***	*de (%)*[a]
1	KHMDS	THF	-78	43:29:28	ND[b]
2	KHMDS	THF	0	>5:36:47	83
3	NaHMDS	THF	-78	64:26:18	88
4	LiHMDS	THF	-78	71:18:11	ND[b]
5	NaH	THF	-78	63:12:25	75
6	KO^{t}Bu	THF	-78	12:>5:83	>95
7	KO^{t}Bu	THF	RT	>5:>5:90[c]	83
8	***KO^{t}Bu***	***THF***	***-78 to RT***	***>5:>5:88***[c]	***>95***

*(a) Ratios determined from examination of the 300 MHz ^{1}H-NMR spectrum of the crude reaction products; (b) de not determined due to low levels of conversion; (c) ^{1}H-NMR analysis also revealed the presence of (S)-4-methyl-oxazolidin-2-one **120**.*

Table 2.1-1 – *Optimisation of the intramolecular cyclisation/elimination reaction of syn-aldol **135** to afford Semiplenamide C **119***

The β-elimination reaction using potassium *tert*-butoxide was then optimised to suppress the formation of oxazolidin-2-one **120**, by carrying out the reaction at -78°C and allowing it to slowly warm to room temperature overnight. This gave *Semiplenamide C* **119** in 74% isolated yield and >95% de with <10% of any other competing side products. The (*E*)-amide **119** afforded spectroscopic data that exactly matched the previously published data for this natural product and gave a specific rotation of $[\alpha]_D^{25} = -8$ ($[\alpha]_D^{lit.} = -5$), thus confirming the absolute configuration of this natural product.[83]



123

Semiplenamide C **119**
74% Yield
>95% de

Reagents and conditions: (i) KO^{t}Bu, THF, -78 to RT overnight.

Scheme 2.1-17 – *Optimised intramolecular elimination reaction for the synthesis of Semiplenamide C*

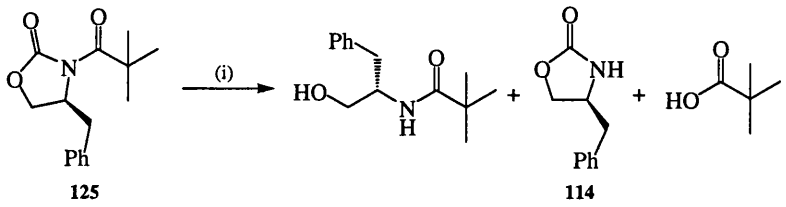
We had therefore completed the total synthesis of *Semiplenamide C* in four steps from commercially available (*S*)-alaninol in 36% overall yield.[84] Application of this methodology to the asymmetric synthesis of the remaining *Semiplenamide* series of natural products is currently underway within the SDB group.

2.1.9 Blocking the intramolecular cyclisation/elimination reactions using the SuperQuat auxiliary

It had been demonstrated that zinc alkoxides and potassium alkoxides of chiral *syn*-aldol substrates could undergo useful cyclisation and elimination reactions to afford oxazinane-2,4-diones and (*E*)-α,β-unsaturated amides respectively. However, the existence of these two competing reaction pathways would prevent the original objective of a new three-step aldol/directed reaction/*retro*-aldol strategy for the

synthesis of *chiral aldehydes* (**Scheme 2.1-2**) from being realised. It was evident that the elimination and cyclisation reactions of *syn*-aldols were due to intramolecular nucleophilic attack of the β-hydroxy alkoxide on the oxazolidin-2-one carbonyl fragment. Therefore, it was proposed that if these unwanted competing reactions could be suppressed, it might result in the desired *retro*-aldol reaction occurring.

It has long been known that the endocyclic carbonyls of oxazolidin-2-ones are susceptible to nucleophilic attack. For example, Davies and co-workers have shown that sterically hindered (*S*)-*N*-pivaloyl-4-benzyl-oxazolidin-2-one **125** underwent competing endocyclic cleavage when treated with lithium hydroxide (**Scheme 2.1-18**).[85]

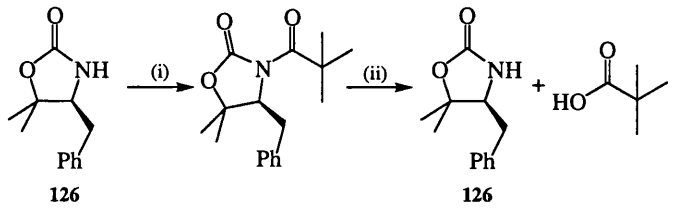


125 **114**

Reagents and conditions: (i) LiOH, THF/H_2O, RT, 2 hours.

Scheme 2.1-18 – *Endocyclic cleavage of N-pivaloyl- oxazolidin-2-ones*

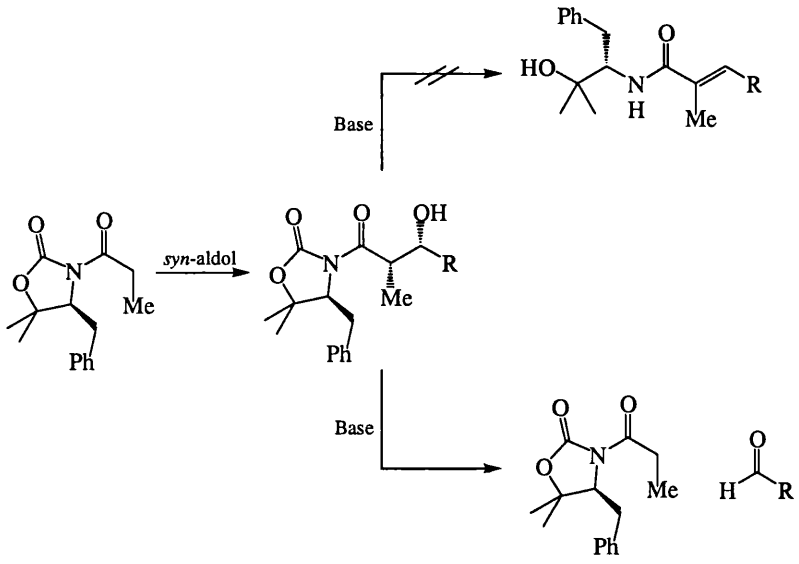
In this instance, the increased steric hindrance of the tertiary butyl group of **125** blocks nucleophilic attack at the exocyclic carbonyl, and as a consequence, competing nucleophilic ring opening of the endocyclic oxazolidin-2-one carbonyl occurs. To address this problem, Davies and co-workers developed a new class of chiral auxiliary, (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one **126**, which were termed as SuperQuat auxiliaries (**Scheme 2.1-19**).[86] They found that the *gem*-dimethyl group of the oxazolidin-2-one ring of the SuperQuat fragment blocks nucleophilic attack at the endocyclic carbonyl, even when the exocyclic carbonyl is sterically hindered, thus affording oxazolidin-2-one **126** as a product of an exclusive exocyclic cleavage pathway.



Reagents and conditions: (i) ^{n}BuLi, pivaloyl chloride, THF; (ii) LiOH, THF/H_2O.

Scheme 2.1-19 – *Exclusive exocyclic cleavage of N-acyl-oxazolidin-2-ones derived from SuperQuat auxiliaries*

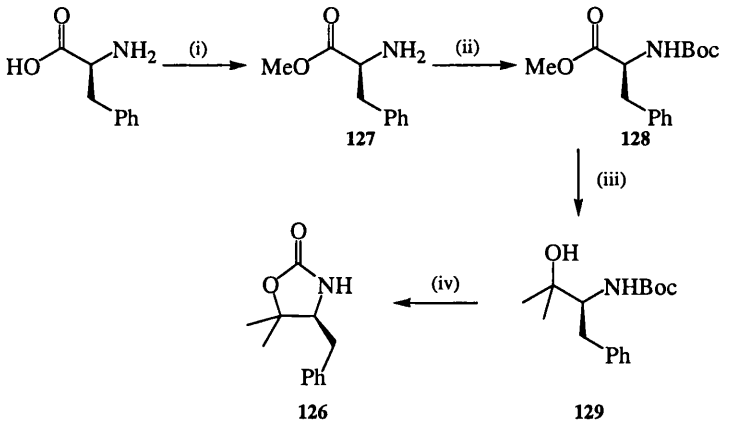
These SuperQuat auxiliaries have been shown to demonstrate the same excellent levels of stereocontrol in *syn*-aldol reactions as previously seen for Evans' auxiliaries.[87] Therefore, it was proposed that these SuperQuat auxiliaries might prove useful for our new three-step *chiral aldehyde* strategy, since it was reasoned that the *gem*-dimethyl substituents of the SuperQuat fragment should also be successful in blocking intramolecular nucleophilic attack at the oxazolidin-2-one carbonyl, thus enabling the desired *retro*-aldol reaction to occur in good yield (**Scheme 2.1-20**).[88]



Scheme 2.1-20 – *Proposed retro-aldol reaction of SuperQuat derived syn-aldols*

2.1.10 Synthesis of the SuperQuat auxiliary

The (*S*)-4-benzyl-oxazolidin-2-one 'SuperQuat' chiral auxiliary **126** was synthesised *via* the standard literature procedure (**Scheme 2.1-21**).[89] Commercially available (*S*)-phenylalanine was esterified *via* formation of its acid chloride with thionyl chloride, which was then trapped *in situ* with methanol, to afford (*S*)-phenylalanine methyl ester **127** in quantitative yield without further purification. *N*-Boc protection of ester **127** *via* treatment with Boc-anhydride and solid sodium hydrogen carbonate afforded **128,** once again in quantitative yield without further purification. Reaction of *N*-Boc ester **128** with excess methyl magnesium iodide afforded tertiary alcohol **129** in 77% yield without further purification. Cyclisation of **129** with potassium *tert*-butoxide, using the *N*-Boc protecting group as a sacrificial carbonyl equivalent, gave (*S*)-4-benzyl SuperQuat oxazolidin-2-one **126** in 55% overall yield from (*S*)-phenylalanine.



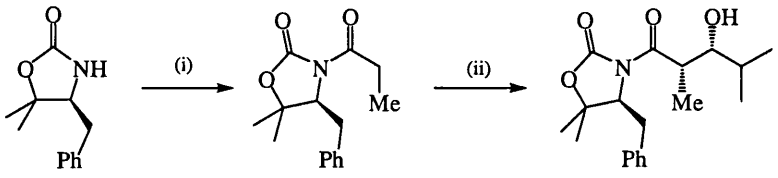
Reagents and conditions: (i) $SOCl_2$, MeOH, 12 hours; (ii) Boc-anhydride, $NaHCO_3$, EtOH, 48 hours; (iii) Mg, CH_3I, THF, 48 hours; (iv) KO^{t}Bu, THF, 2 hours.

Scheme 2.1-21 – *Synthesis of the SuperQuat chiral oxazolidin-2-one*

2.1.11 Aldol reactions of SuperQuat auxiliaries

It was then necessary to demonstrate that SuperQuat chiral auxiliaries would give comparable results to standard Evans' auxiliaries for *syn*-aldol reactions. As a model

system, we carried out the *syn*-aldol reaction of (*S*)-4-benzyl *N*-propionyl-oxazolidin-2-one SuperQuat chiral auxiliary **130** with isobutyraldehyde (**Scheme 2.1-22**). (*S*)-4-Benzyl-*N*-propionyl SuperQuat oxazolidin-2-one **130** was generated *via* acylation of the *N*-lithium anion of **126** with propionyl chloride in 89% yield. The boron aldol reaction of **130** with isobutyraldehyde gave α-methyl-β-isopropyl *syn*-aldol **131** in 82% yield and >95% de as determined by examination of the crude ^{1}H-NMR spectrum. The stereochemistry was assigned from literature precedent, and confirmed by the small α-proton coupling constant of $J_{2,3}$ = 3.0 Hz.



126 | **130** 89% Yield | **131** 82% Yield >95% de

Reagents and conditions: (i) ^{n}BuLi, propionyl chloride, THF, -78°C to 0°C, 2 hours; (ii) 9BBN-OTf, ^{i}Pr$_2$NEt, CH_2Cl_2, 0°C, 1 hour, isobutyraldehyde, -78°C 1 hour then 0°C 1 hour.

Scheme 2.1-22 – *syn-Aldol reaction of SuperQuat auxiliary*

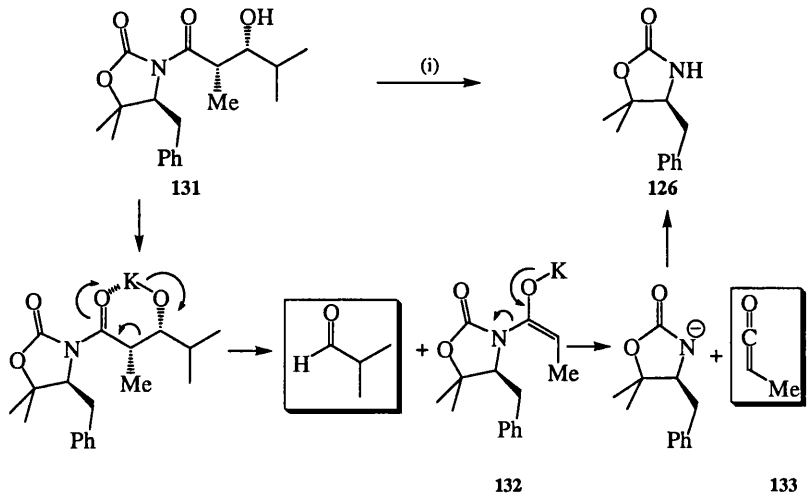
2.1.12 Attempted *retro*-aldol reactions of SuperQuat aldols

Having demonstrated that the SuperQuat auxiliary afforded *syn*-aldol results comparable to the standard Evans' auxiliary, it was then necessary to examine whether the increased steric hindrance of the SuperQuat auxiliary fragment would suppress the intramolecular rearrangement/β-elimination pathway. α-Methyl-β-isopropyl *syn*-aldol **131** was therefore treated with 10mol% diethyl zinc under our standard cyclisation conditions.

Analysis of the crude ^{1}H-NMR spectrum revealed that treatment of α-methyl-β-isopropyl *syn*-aldol **131** with 10 mol% diethyl zinc at room temperature had resulted in the formation of less than 10% of its corresponding 1,3-oxazinane-2,4-dione product after two hours, indicating that the *gem*-dimethyl group of the oxazolidin-2-

one fragment of **131** had significantly reduced the rate of the diethyl zinc mediated rearrangement reaction.

Alternatively, treatment of *syn*-aldol **131** with KHMDS at -78°C in THF resulted in no reaction occuring, affording only recovered starting material. Repeating the reaction at room temperature produced a crude ^{1}H-NMR spectrum that contained (*S*)-4-benzyl SuperQuat oxazolidin-2-one **126** with no other compounds being observed, including the initially expected *N*-propionyl-oxazolidin-2-one **130**. It was proposed that formation of the parent oxazolidin-2-one **126** was arising due to *syn*-aldol **131** undergoing a *retro*-aldol reaction, followed by decomposition of the resultant potassium enolate **132** *via* a *retro*-ketene type pathway to generate oxazolidin-2-one **126**. Isobutyraldehyde and methyl ketene **133** would not be expected to be observed in the crude ^{1}H-NMR due to their inherent volatility (**Scheme 2.1-23**).[90] No corresponding elimination or cyclisation products were observed under either the diethyl zinc or KHMDS conditions, indicating that the *gem*-dimethyl substituents of the SuperQuat auxiliary were functioning as intended.

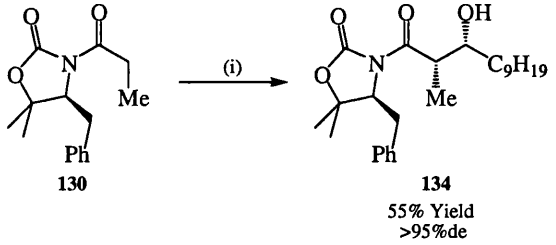


Reagents and conditions: (i) KHMDS, THF, RT, 2 hours.

Scheme 2.1-23 – *Proposed retro-aldol/retro-ketene decomposition pathway of the potassium enolate of N-propionyl-oxazolidin-2-one*

2.1.13 Optimisation of the *retro*-aldol reaction

Having demonstrated that SuperQuat oxazolidin-2-one derived *syn*-aldol **131** underwent *retro*-aldol reactions without any competing rearrangement pathways under basic conditions, it was then necessary to demonstrate that the aldehyde could be isolated in from the *retro*-aldol reaction high yield. α-Methyl-β-nonyl *syn*-aldol **134** was therefore synthesised *via* reaction of the boron enolate of *N*-propionyl SuperQuat oxazolidin-2-one **130** with decanal under our standard conditions to afford *syn*-aldol **134** in 55% yield and >95% de. (**Scheme 2.1-24**).



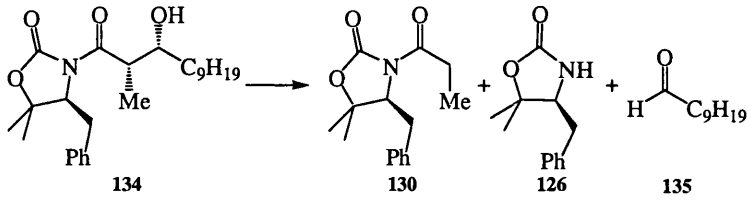
Reagents and conditions: (i) 9BBN-OTf, $^{i}Pr_2NEt$, CH_2Cl_2, 0°C, 1 hour, decanal, -78°C, 1 hour then 0°C, 1 hour.

Scheme 2.1-24 – *syn-Aldol reaction of decanal*

It was reasoned that the *retro*-aldol reaction of *syn*-aldol **134** would result in formation of the *N*-acyl-oxazolidin-2-one fragment and the relatively non-volatile decanal, thus enabling it to be observed in the ^{1}H-NMR spectra of the crude reaction product. Treatment of *syn*-aldol **134** with KHMDS at -78°C in THF gave no reaction once again affording only starting material **134** and consequently, a range of bases and conditions were screened to optimise this *retro*-aldol reaction (**Table 2.1-2**).

The majority of these screening reactions (**Entries 1-8, 12**), gave very poor yields of the desired decanal **135**; however, the use of LiHMDS as a base at 0°C to 10°C did give acceptable yields of decanal **135**. From these results, it was apparent that the amount of decanal formed in the *retro*-aldol reaction was directly proportional to the amount of *N*-propionyl-oxazolidin-2-one **130** present in the crude ^{1}H-NMR spectra. Conversely, any formation of SuperQuat oxazolidin-2-one **126** appeared to result in a matched loss in yield of decanal product **135**. This observation was difficult to justify,

since no other products were observed in the crude ^{1}H-NMR spectra of these reactions, and despite repeated attempts, no alternative products could be isolated from either organic or aqueous extracts.



134 130 126 135

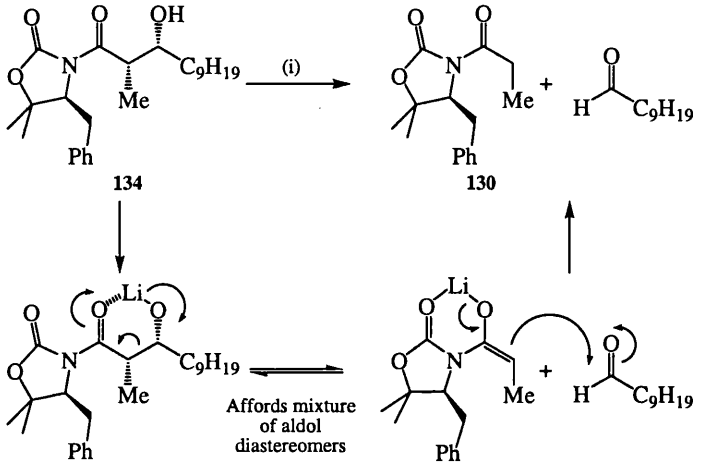
Entry	*Base*[a]	*Temp. (°C)*[b]	*Solvent*	*Product Ratio*[c] ***130:126:135***
1	KHMDS	-78	THF	NR[d]
2	KHMDS	-40	THF	NR[d]
3	KHMDS	0	THF	10:82:8
4	KHMDS	RT	THF	<5:95:<5
5	NaH	0	THF	<5:95:<5
6	KO^{t}Bu	0	THF	<5:95:<5
7	KO^{t}Bu/HO^{t}Bu	0	THF	<5:95:<5
8	LiHMDS	-40	THF	NR[e]
9	LiHMDS	0	THF	30:45:25
10	LiHMDS	0	Toluene	33:35:32[f]
11	LiHMDS	10	Toluene	31:37:32
12	LiHMDS	RT	Toluene	8:85:7

*(a) 1.1 equivalents of base; (b) All reactions were carried out over a period of 2 hours; (c) Product ratio determined by examination of the crude ^{1}H-NMR spectra; (d) Reaction displayed clean spectra of **126**; (e) ^{1}H-NMR indicated a mixture of aldol diastereomers; (f) Reaction failed to go to completion.*

Table 2.1-2 – *Optimisation of the retro-aldol reaction of β-alkyl syn-aldol*

Consideration of these results revealed that employing the more aggregating lithium counter-ion (compare **Entry 3** with **Entry 9**) and the more aggregating toluene solvent, (compare **Entry 9** with **Entry 10**), had resulted in an improved yield of aldehyde isolated from these *retro*-aldol reactions. It was also clear that temperature played a key role in the success of this *retro*-aldol reaction (**Scheme 2.1-25**). Treatment of *syn*-aldol **134** with LiHMDS at -78°C resulted in no *retro*-aldol reaction occurring; however, as the temperature was increased to -40°C, the reaction resulted in a crude ^{1}H-NMR spectrum that was extremely complicated, which was tentatively justified as the *retro*-aldol reaction becoming reversible (**Scheme 2.1-25**), resulting in a mixture of the aldol diastereomers derived from *syn*-aldol **134**. This was indicated

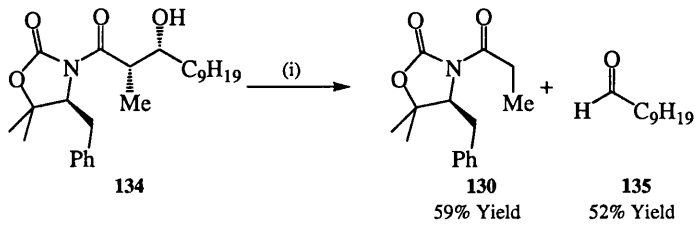
by the appearance of two new resonances in the ^{1}H-NMR spectrum of the crude reaction mixture at δ4.56 ppm and δ4.60 ppm, which were assigned as the C4 protons of the oxazolidin-2-one fragment of each diastereomer. This diastereomeric mixture presumably forms due to the well-known poor stereocontrol of lithium enolates in this type of asymmetric aldol reaction.[91] The LiHMDS mediated *retro*-aldol reaction of **134** was then carried out at 0°C, which gave an increased conversion to the desired *retro*-aldol products at this temperature. It is likely that a reversible *retro*-aldol reaction also occurs at 0°C; however, the equilibrium at this temperature clearly lies towards the *retro*-aldol cleavage products.



Reagents and conditions: (i) LHMDS, toluene, 0°C, 2 hours.

Scheme 2.1-25 – *Proposed mechanism for the reversible retro-aldol reaction of syn-aldol **134** with LiHMDS in toluene*

The *retro*-aldol reaction was therefore optimised at 10°C, where it became the major reaction pathway affording *N*-propionyl-oxazolidin-2-one **130** and decanal in 59% and 52% yield respectively (**Scheme 2.1-26**). Above this temperature, it was found that SuperQuat oxazolidin-2-one **126** became the major product, and under these conditions very low yields of decanal **135** were observed (**Entry 12**).



Reagents and conditions: (i) LiHMDS, toluene, 10°C, 2 hours.

Scheme 2.1-26 – *Optimised retro-aldol reaction for β-alkyl syn-aldol* ***134***

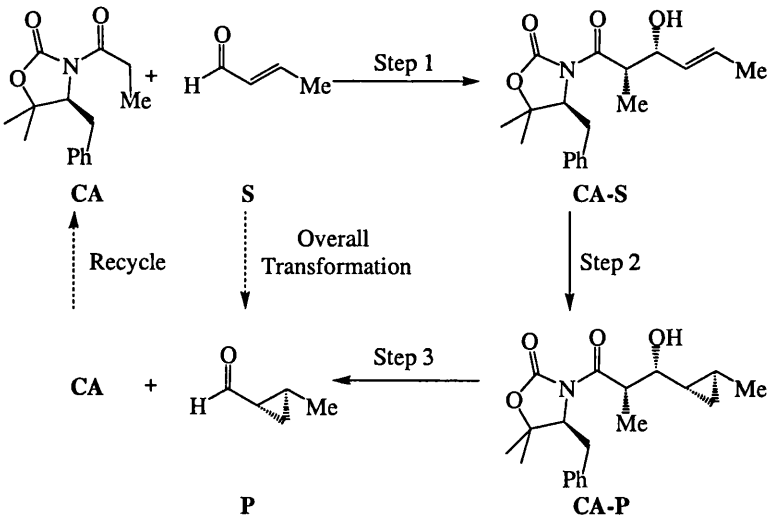
2.1.14 Conclusions

It has been demonstrated that chiral oxazolidin-2-one derived *syn*-aldols can undergo novel intramolecular cyclisation and elimination reactions with excellent levels of diastereocontrol, and applied this methodology to the synthesis of chiral oxazinane-2,4-diones and the first total synthesis of *Semiplenamide C*. These unwanted reaction pathways were suppressed using *syn*-aldols derived from SuperQuat chiral auxiliaries, due to the presence of a *gem*-dimethyl substituent that prevents intramolecular nucleophilic attack of the alkoxide species at the oxazolidin-2-one carbonyl. As a consequence, conditions were established enabling lithium alkoxides of this type of *syn*-aldol to undergo *retro*-aldol reactions, affording their corresponding aldehydes in acceptable yields.

Chapter 2.2 A novel protocol for the asymmetric synthesis of cyclopropane carboxaldehydes

2.2.1 Introduction

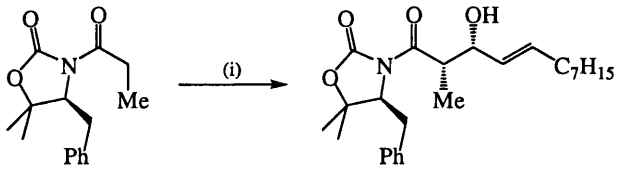
In this chapter the asymmetric synthesis of a range of unsaturated *syn*-aldols derived from *N*-propionyl-oxazolidin-2-ones, which are then used as substrates for stereoselective hydroxyl directed cyclopropanation reaction, will be described. The optimised *retro*-aldol reaction of cyclopropane *syn*-aldols is then discussed, which completes the novel three-step strategy for the asymmetric synthesis of *chiral aldehydes* (**Scheme 2.2-1**).



Scheme 2.2-1 – *Novel three-step strategy for the asymmetric synthesis of chiral aldehydes*

2.2.2 Optimisation of the asymmetric *syn*-aldol reaction of (*E*)-α,β-unsaturated aldehydes

Having developed conditions that enable aldol and *retro*-aldol reactions to be carried out in acceptable yields, our three-step synthesis of *chiral aldehydes* required access to a series of β-vinyl *syn*-aldol products that could be used for hydroxyl directed cyclopropanation reactions. For reasons discussed in the previous chapter, the boron enolate of (*S*)-4-benzyl-*N*-propionyl-5,5-dimethyl-oxazolidin-2-one **130** was chosen as a chiral auxiliary for the *syn*-aldol reaction with (*E*)-dec-2-enal.[92] Unfortunately, under our previously optimised reaction conditions for aliphatic aldehydes, (*E*)-α-methyl-β-vinyl *syn*-aldol **137b** could only be isolated in a disappointing 38% yield with the remaining mass balance comprising starting material (**Scheme 2.2-2**).



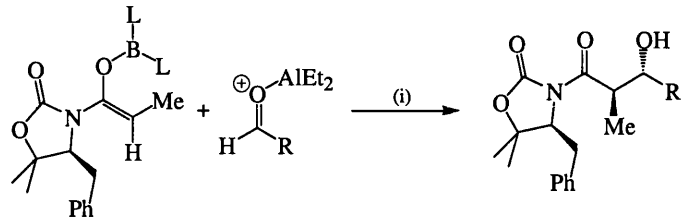
130 **137b**
38% Yield
>95%de

Reagents and conditions: (i) 9BBN-OTf, $^{i}Pr_2NEt$, CH_2Cl_2, 0°C, 1 hour, (E)-dec-2-enal, -78°C, 1 hour then 0°C 1 hour.

Scheme 2.2-2 – *Boron mediated syn-aldol reaction of α,β-unsaturated aldehydes*

It was proposed that the decreased yield of *syn*-aldol product **137b** was a result in this instance of the lower reactivity of (*E*)-dec-2-enal **136b** when compared to isobutyraldehyde, arising from conjugation of the aldehyde functionality with the alkene. In an attempt to increase the yield of the reaction, the stoichiometry of the *syn*-aldol reaction was altered. Using two equivalents of 9BBN-triflate increased the yield of *syn*-aldol **137b** to 75%, but lowered the diastereoselectivity to 81% de. This observation was not totally unexpected, since Heathcock and Walker had previously shown that pre-coordination of an aldehyde with a Lewis acid, prior to reaction with

the boron enolate had the potential to change the diastereoselectivity of the aldol reaction from *syn*- to *anti*-selective (**Scheme 2.2-3**).[93]



Reagents and conditions: (i) Dibutyl boron triflate, $^{i}Pr_2NEt$, CH_2Cl_2, 0°C, 1 hour, then aldehyde/Et_2AlCl, -78°C, 5 hours.

Scheme 2.2-3 – *Heathcock's Lewis acid mediated anti-aldol reaction*

In this case, it was proposed that coordination of the Lewis acid to the aldehyde creates an acyclic transition state (**Figure 2.2-1**), which in contrast to the Zimmerman-Traxler transition state shown previously (**Scheme 2.1-7**), affords the *anti*-aldol as the major product in good yield.

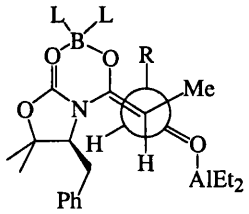


Figure 2.2-1 – *Acyclic transition state of Lewis acid mediated anti-aldol reaction*

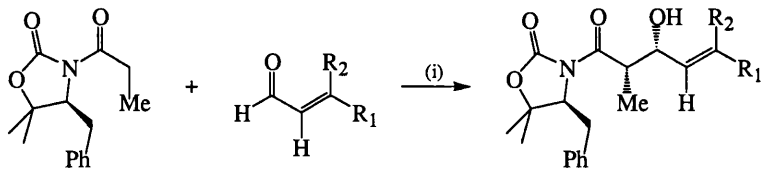
It was believed that the second unreacted equivalent of 9BBN-triflate in our reaction might be acting as a Lewis acid in this manner by coordinating to the aldehyde, thus reducing the overall diastereoselectivity of the reaction. Increasing the amount of base, diisopropylethylamine, used in this aldol reaction had little effect on the conversion, whilst increasing the stoichiometry of the aldehyde to two equivalents decreased the diastereoselectivity to 90%, whilst only increasing the conversion to 65%. Therefore, it was clearly necessary to maintain the stoichiometry of the aldol

reaction at a ratio of at one equivalent of aldehyde to one equivalent of 9BBN-triflate and diisopropylethylamine in order to achieve high diastereoselectivity.

The reaction time and temperature were then investigated. The (*Z*)-boron enolate of **130** was generated at 0°C for one hour before the reaction was cooled to -78°C and (*E*)-dec-2-enal **136b** added. The reaction was then allowed to slowly warm to room temperature overnight. This afforded *syn*-aldol **137b** in an acceptable 77% yield and >95% de. Therefore, it would appear that the decrease in concentration of aldehyde as the *syn*-aldol reaction proceeds is matched by the increase in reaction temperature, which serves to maintain the reactivity and diastereoselectivity of the reaction under these conditions.

2.2.3 Synthesis of a series of α-methyl (*E*)-β-vinyl *syn*-aldols

Using these optimised *syn*-aldol conditions, it proved possible to synthesise a series of chiral unsaturated aldol substrates in 76% to 87% yield and in >95% de in all cases (**Table 2.2-1**). Therefore, A range of commercially available α,β-unsaturated aldehydes containing aryl (electron withdrawing and donating), heteroaryl and alkyl substituents all afforded *syn*-aldol products in good yield and excellent de. The *syn*-configuration of these aldol products were confirmed from their small $J_{2,3}$ coupling constants between 4.0 Hz and 5.0 Hz.



Entry	*Aldehyde*	*R_1*	*R_2*	*de (%)[a]*	*Aldol*	*Yield (%)*
1	**136a**	Ph	H	>95	**137a**	80
2	**136b**	$Me(CH_2)_6$-	H	>95	**137b**	81
3	**136c**	*p*-MeOPh-	H	>95	**137c**	77
4	**136d**	*o*-NO_2Ph-	H	>95	**137d**	87
5	**136e**	2-Furyl-	H	>95	**137e**	85
6	**136g**	Me	H	>95	**137g**	76
7	**136h**	Me	Me	>95	**137h**	76

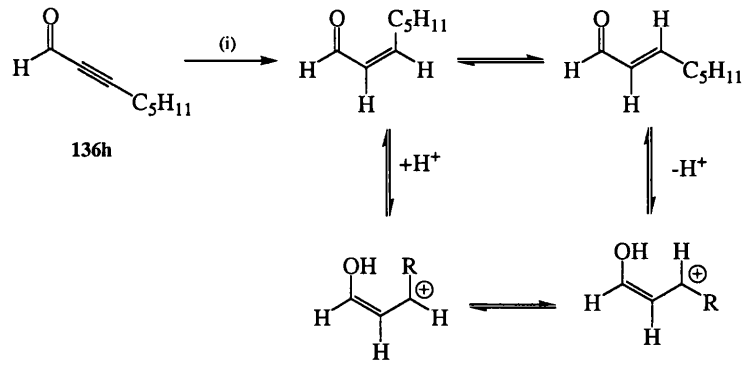
Reagents and conditions: 9BBN-OTf, $^iPr_2NEt$, CH_2Cl_2, 0°C, 1 hour, α,β-unsaturated aldehyde, -78°C to RT, overnight;

(a) Determined by examination of the crude ^{1}H-NMR spectra.

Table 2.2-1 – *syn-Aldol reactions of (E)-α,β-unsaturated aldehydes*

2.2.4 Synthesis of an α-methyl (*Z*)-β-vinyl *syn*-aldol

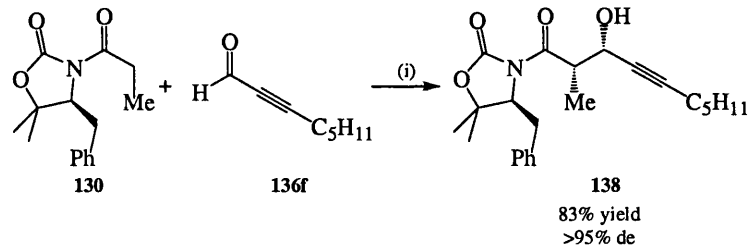
In order to complete the series of unsaturated aldol substrates, it was necessary to synthesise a (*Z*)-unsaturated *syn*-aldol. (*Z*)-α,β-unsaturated aldehydes are known to be unstable under mildly acidic conditions and this was confirmed by attempted Lindlar's hydrogenation of oct-2-ynal **136h**, which generated an inseparable mixture of (*E*) and (*Z*) isomers (**Scheme 2.2-4**).[94] It is likely that the (*Z*)-isomer is initially formed in this reaction in this hydrogenation reaction, but that it rapidly isomerised to its thermodynamically more stable (*E*)-isomer in the presence of adventitious acid.



Reagents and conditions: (i) Lindlar's catalyst, H_2 (1 atm), MeOH.

Scheme 2.2-4 – *Isomerisation of (Z)-α,β-unsaturated aldehydes under acidic conditions*

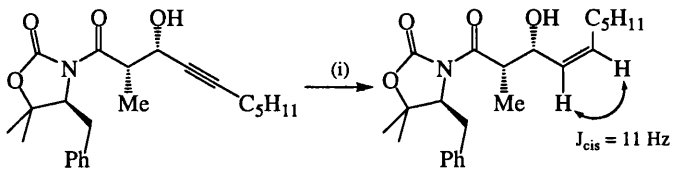
An alternative strategy to this class of *syn*-aldol was therefore devised involving the aldol reaction of the boron enolate of *N*-propionyl SuperQuat oxazolidin-2-one **130** with oct-2-ynal **136f**, which under our previously described optimised conditions, afforded the desired α-methyl β-alkynyl *syn*-aldol **138** in 83% yield and >95% de (**Scheme 2.2-5**).[95]



Reagents and conditions: (i) 9BBN-OTf, $^iPr_2NEt$, CH_2Cl_2, 0°C, 1 hour, oct-2-ynal, -78°C to RT overnight.

Scheme 2.2-5 – *Asymmetric syn-aldol reaction of oct-2-ynal*

β-alkynyl *syn*-aldol **138** was then hydrogenated with Lindlar's catalyst under one atmosphere of hydrogen for one hour in methanol,[96] to afford exclusively the (Z)-diastereomer of *syn*-aldol **137f** in quantitative yield (**Scheme 2.2-6**).[97] The *cis*-stereochemistry of the alkene fragment was clearly evident from the coupling constant of 11Hz between the alkene protons.



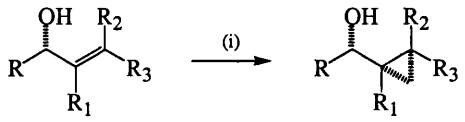
138 **137f**
93% Yield
>95% de

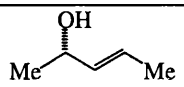
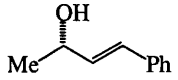
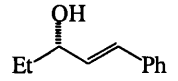
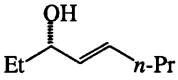
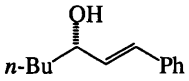
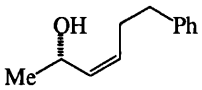
Reagents and conditions: 10 mol% Lindlar's Catalyst, 1 atm H_2, MeOH, 2 hours.

Scheme 2.2-6 – *Lindlar's hydrogenation of α-methyl β-alkynyl syn-aldol*

2.2.5 Directed cyclopropanation reaction of β-vinyl-*syn*-aldols

With a variety of β-vinyl *syn*-aldol substrates in hand, it was then necessary to carry out a stereoselective substrate directable transformation on these compounds and therefore complete *step 2* of our new three-step synthesis of *chiral aldehydes*. A review of the literature revealed that the hydroxyl directed cyclopropanation reaction of allylic alcohols had been shown previously to proceed with excellent diastereoselective control.[98] Under modified Furukawa's conditions, Charette and co-workers cyclopropanated a variety of chiral allylic alcohols with >100:1 diastereoselectivity and in excellent yield (**Table 2.2-2**).[99]



Entry	*Allylic Alcohol*	*Yield*	*syn:anti ratio*
1		75	6:1
2		86	7:1
3		97	130:1
4		87	110:1
5		98	150:1
6		96	>200:1

Reagents and conditions: (i) Et_2Zn, CH_2I_2, CH_2Cl_2, -10 to 0°C, 2 hours

Table 2.2-2 – *Directed cyclopropanation of allylic alcohols*

Five equivalents of diethyl zinc and diiodomethane were required to ensure complete consumption of the olefin substrate in these reactions. The results demonstrate that excellent levels of diastereocontrol could be achieved for a wide range of allylic alcohols, containing various substituents at their 3-position.[100] A proposed *pseudo*-pericyclic mechanism for this hydroxyl directed cyclopropanation reaction is shown in **Figure 2.2-2**.[101] Deprotonation of the allylic alcohol functionality forms an alkoxide species containing two zinc atoms, which then serves as the cyclopropanating reagent. This reagent acts as a carbenoid equivalent that delivers a methylene unit to one face of the olefin. It is known that the hydroxyl group plays a vital role in the diastereoselectivity of the reaction, since in its absence, a simple olefin is cyclopropanated at a rate approximately 1000 times slower than for an allylic alcohol.[101]

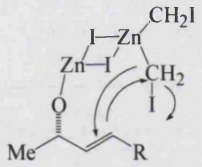
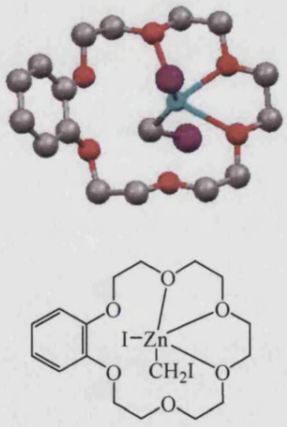


Figure 2.2-2 – *Proposed mechanism for the cyclopropanation of allylic alcohols*

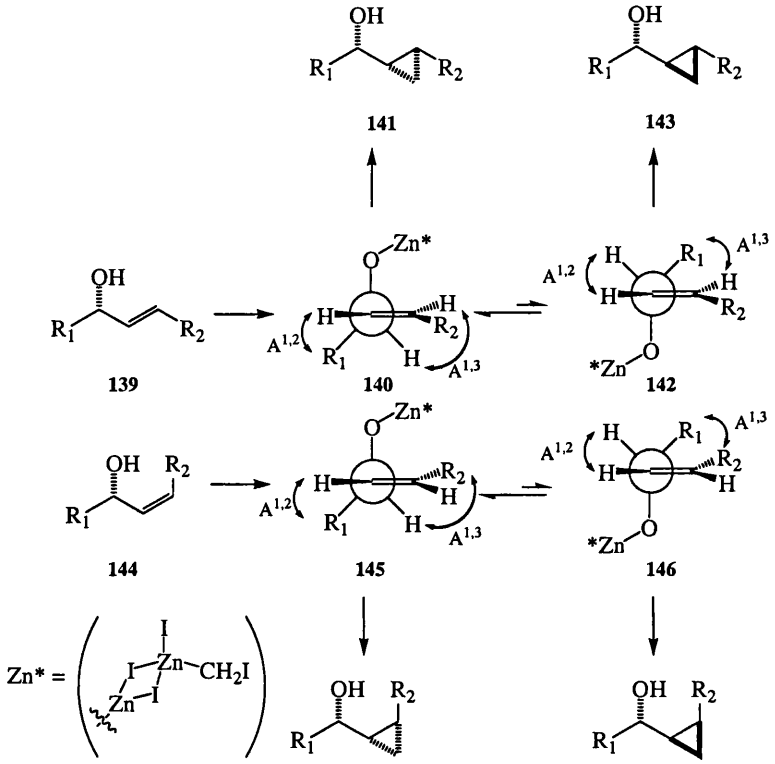
The nature and stoichiometry of the reagents used to generate the cyclopropanating species is also important in determining the diastereoselectivity of the reaction. Originally, the Simmons-Smith cyclopropanation reaction was carried out with activated metallic zinc to generate the methylene carbenoid equivalent.[102] These conditions have largely been superseded by the use of Furukawa's reagent, due to the greater consistency of results achieved.[103] Diethyl zinc and diiodomethane react *via* halogen-metal exchange to afford an iodomethyl zinc iodide species *in-situ*, whose precise structure is dependent on the stoichiometry of the reagents. Three reactive species have been proposed for the reagents generated under these conditions; $IZnCH_2I$, $Zn(CH_2I)_2$ and $EtZnCH_2I$. A structure of the proposed reactive cyclopropanating species $IZn(CH_2I)$, which was co-crystallised with benzo-18-crown-6-ether, has been elucidated *via* X-ray crystallographic studies (**Figure 2.2-3**).[104]



Hydrogens omitted for clarity; Red = Oxygen, Grey = Carbon, Purple = Iodine, Turquoise = Zinc.

Figure 2.2-3 – *X-ray crystal structure of $IZnCH_2I$•benzo-18-crown-6-ether*

Whichever reactive species is responsible for the stereoselective cyclopropanation,[105] it is inevitably minimisation of allylic strain in the transition state that determines the diastereoselectivity of the reaction. Coordination of the carbenoid cyclopropanating species to the stereodirecting hydroxyl group is then responsible for establishing which of the diastereotopic faces of the olefin is cyclopropanated.

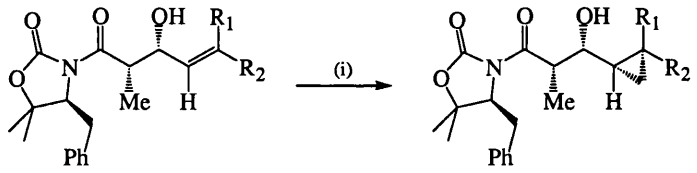


Scheme 2.2-7 – *Minimisation of allylic strain in the cyclopropanation of allylic alcohols*

Upon reaction of the allylic alcohol with the cyclopropanating reagent, the methylene carbenoid can be delivered to either of the two diastereotopic faces of the olefin. Transition state **140** arising from *trans*-allylic alcohol **139** places the sterically hindered R_1 group adjacent to the proximal olefinic hydrogen atom resulting in $A^{1,2}$-strain; whilst positioning the sterically hindered distal alkenyl hydrogen close to the C_1 hydrogen atom, resulting in $A^{1,3}$-strain. This reactive conformation will lead to the formation of the *syn*-cyclopropyl alcohol **141**. Rotating the C_1-C_2 bond affords conformer **142** that allows the hydroxyl group to direct cyclopropanation to the opposite diastereotopic face of the olefin. However, whilst this conformer positions

the C_1 hydrogen atom and the olefinic hydrogen atom close together, resulting in minimisation of $A^{1,2}$-strain, it also places the sterically hindered R_1 group close to the distal alkenyl proton, maximising $A^{1,3}$-strain. Therefore, transition state **142**, leading to the *anti*-cyclopropyl alcohol **143**, is higher in energy than transition state **140** and as a consequence, *syn*-selectivity is observed. This stereodirecting effect is even more apparent for *cis*-allylic alcohol **144**, since the energy difference between transition states **145** and **146** is increased by the R_2 group pointing towards the R_1 group, thus increasing $A^{1,3}$-strain even further.

It was decided to apply this type of highly diastereoselective hydroxyl directed cyclopropanation reaction to our prochiral unsaturated oxazolidin-2-one *syn*-aldol substrates. Therefore, the previously prepared *syn*-aldols **137a** to **137h** were treated with five equivalents of diethyl zinc and diiodomethane under Charette's conditions **(Table 2.2-3)**



Entry	*Aldol*	*R_1*	*R_2*	*Cyclopropyl Aldol*	*Time (hrs)*	*de[a] (%)*	*Yield (%)*
1	**137a**	H	Ph	**147a**	1	>95	95
2	**137b**	H	*n*-C_8H_{17}	**147b**	1	>95	89
3	**137c**	H	*p*-PhOMe	**147c**	1	>95	90
4	**137d**	H	*o*-$PhNO_2$	**147d**	1	>95	90
5	**137e**	H	2-Furyl	**147e**	2	>95	92
6	**137f**	*n*-C_5H_{11}	H	**147f**	2	>95	96
7	**137g**	H	Me	**147g**	4	>95	95
8	**137h**	Me	Me	**147h**	2	>95	92

Reagents and conditions: (i) Et_2Zn, CH_2I_2, CH_2Cl_2, -10 to 0°C

(a) Determined from examination of the crude 300 MHz ^{1}H-NMR spectra

Table 2.2-3 – *Cyclopropanation of α-methyl β-vinyl oxazolidin-2-one syn-aldols*

Under these conditions, it was demonstrated that the hydroxyl directed cyclopropanation reaction proceeded with excellent diastereoselectivity, regardless of the type of alkene substituents present in the aldol substrate. Examination of the crude

300 MHz ^{1}H-NMR spectra of each cyclopropanation reaction revealed no evidence of any *anti*-cyclopropane diastereomer and as a consequence, the stereocontrol was assigned as >95% de in favour of the *syn*-diastereomer. The yields obtained of cyclopropane aldols **147a-147h** obtained in these cyclopropanation reactions were excellent in all cases, with the crude products found to be near analytical purity after work-up, requiring only simple chromatography to remove residual diiodomethane. α-Methyl nitrophenyl cyclopropyl *syn*-aldol **137d** (**Entry 7**) required increased reaction times to ensure complete consumption of the starting aldol **137d**. This is likely to be a result of the electron deficient nature of its olefin substituent, caused by the presence of the electron withdrawing *ortho*-nitrophenyl functionality. No evidence of any products arising from a competing cyclisation pathway to their corresponding 1,3-oxazinane-2,4-diones (**Scheme 2.1-14**), or subsequent E1$_c$b elimination to their corresponding α,β-unsaturated amides (**Scheme 2.1-11**) was observed in any of these reactions, thus demonstrating the effectiveness of the SuperQuat auxiliary in blocking these competing reaction pathways.

The cyclopropane rings of these aldol substrates were easily identified in their ^{1}H-NMR spectra due to the high field chemical shifts observed for their cyclopropyl protons, which has been attributed to the sigmatropic aromaticity of the cyclopropane ring. The Walsh model[106] describes cyclopropane bonding as being constructed from three sp^2 hybridised orbitals, for which the basis set is shown in **Figure 2.2-4.** The sp^2 hybrid orbitals are pointed towards the centre of the ring, resulting in diminished overlap, which also serves to explain the increased reactivity of the cyclopropane ring.

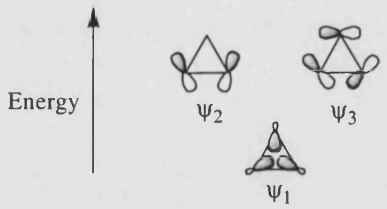
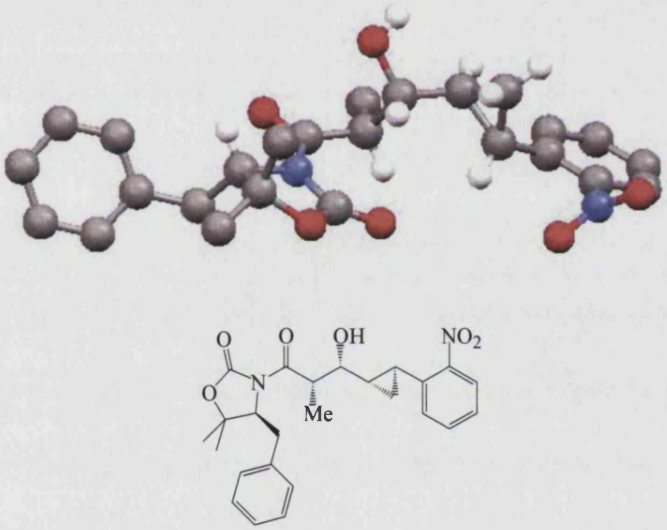


Figure 2.2-4 – *Walsh's basis set for the bonding in cyclopropane*

The high field chemical shift of the cyclopropane protons can be explained through this model by considering sigmatropic aromaticity. Occupation of ψ_1 results in a three-centre two-electron bond.[107] This sigmatropic resonance complies with the 4n+2 rule for aromaticity around the three-membered ring, which creates a ring current that shields the cyclopropyl protons from the applied magnetic field. In the absence of electron withdrawing groups, the cyclopropane protons are characteristically observed in the 0 to 1 ppm region of their ^{1}H-NMR spectra.

The all *syn*-stereochemistry of cyclopropane *syn*-aldols **147a-147h** were assigned from literature precedent for this class of cyclopropanation reaction (**Scheme 2.2-7**), and was confirmed for the crystalline nitrophenyl-α-methyl-β-cyclopropyl *syn*-aldol **147d** by X-ray crystallographic studies (**Figure 2.2-5**).



Selected hydrogens omitted for clarity; Red = Oxygen, Grey = Carbon, Purple = Nitrogen, White = Hydrogen.

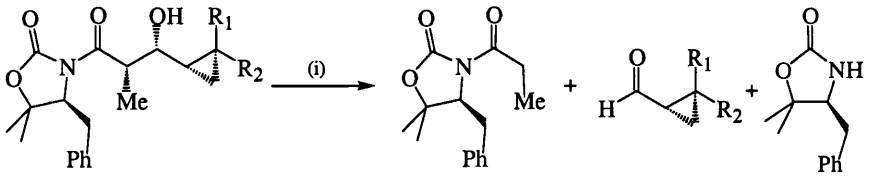
Figure 2.2-5 – *X-ray crystal structure of nitrophenyl-α-methyl-β-cyclopropyl syn-aldol* ***147d***

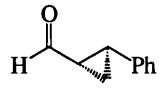
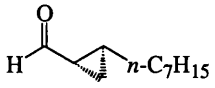
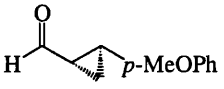
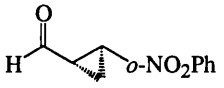
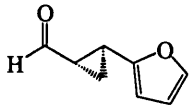
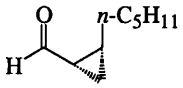
This crystal structure clearly revealed the all *syn*-stereochemistry of the *N*-acyl fragment caused by delivery of the methylene carbenoid to the alkene functionality of **137d** by its hydroxyl group.

2.2.6 *Retro*-aldol reaction of β-cyclopropyl-*syn*-aldols to afford non-volatile cyclopropane carboxaldehydes

To compete our new three-step synthesis of *chiral aldehydes*, it was necessary to carry out *retro*-aldol reactions on our cyclopropyl *syn*-aldol substrates. Therefore, β-cyclopropyl-*syn*-aldols **147a-147h** were subjected to the *retro*-aldol conditions we had established previously for *syn*-aldol **134** involving treatment with LiHMDS in toluene (see **Scheme 2.1-25**).

The results of the *retro*-aldol reactions carried out are described in **Table 2.2-4**.[108] It became apparent that the success of these *retro*-aldol reactions was highly dependent on the temperature at which the reaction was performed. It was found that the *retro*-aldol reaction of each cyclopropyl aldol substrate had to be optimised to maximise the conversion to the required aldehyde. For example, the *retro*-aldol reaction of *syn*-aldol **147a** (**Entry 1**) when carried out at -20°C, unreacted starting material was recovered as the major product, with less than 10% of any *retro*-aldol products being observed; when the temperature was increased to 20°C, the major product recovered was oxazolidin-2-one **126**, again with less than 10% of any *retro*-aldol reaction products being observed. Only at the optimised temperature of 0°C could cyclopropane carboxaldehyde **148a** be isolated in an acceptable 75% yield. Following the course of this *retro*-aldol reaction *via* thin layer chromatography, in an attempt to identify when the cyclopropane *syn*-aldol had been consumed proved unsuccessful. This was because the aliquot taken for analysis warmed to room temperature when it was removed from the reaction mixture, and as a consequence the analysis did not reflect the mixture of products obtained upon quenching these *retro*-aldol reactions.



Entry	*Aldol*	*Aldehyde*	*Temp. (°C)*	*de (%)[a]*	*Yield (%)*	*$[\alpha]_D^{25}$*
1	**147a**	 **148a**	0	>95	75	+392[b] ($Lit_{(R,R)}$ = -324)
2	**147b**	 **148b**	0	>95	73	+45[b] ($Lit_{(S,S)}$ = +41)
3	**147c**	 **148c**	0	>95	63	+228[c]
4	**147d**	 **148d**	5	>95	55	+110[c]
5	**147e**	 **148e**	10	>95	71	+320[c]
6	**147f**	 **148f**	0	>95	61	-10[d]

Reagents and conditions: (i) LHMDS, toluene, 2 hours.

(a) Determined by examination of the crude 300 MHz ^{1}H-NMR spectra; (b) Run in $CHCl_3$ and were comparable with known literature values (see reference 108); (c) Run in CH_2Cl_2; (d) Run in $CHCl_3$, specific rotation was comparable with structurally related (1S,2R)-2-hexylcyclopropanecarbaldehyde (see reference 108).

Table 2.2-4 – *Retro-aldol reaction of cyclopropyl syn-aldols*

Analysis of the crude ^{1}H-NMR spectra of successful *retro*-aldol reactions once again displayed a clear proportionality between the amount of cyclopropane carboxaldehyde isolated and the amount of *N*-acylated oxazolidin-2-one **130** formed. Similarly, formation of any oxazolidin-2-one **126**, presumably *via* a *retro*-ketene

decomposition pathway, was always associated with a proportional loss in the amount of desired cyclopropane carboxaldehyde (**Appendix 4.1**). No other products were observed in the crude 300 MHz ^{1}H-NMR spectra of any *retro*-aldol reactions, and despite repeated attempts, I was unable to isolate any by-products from these reactions that might be responsible for consuming the aldehyde fragment.

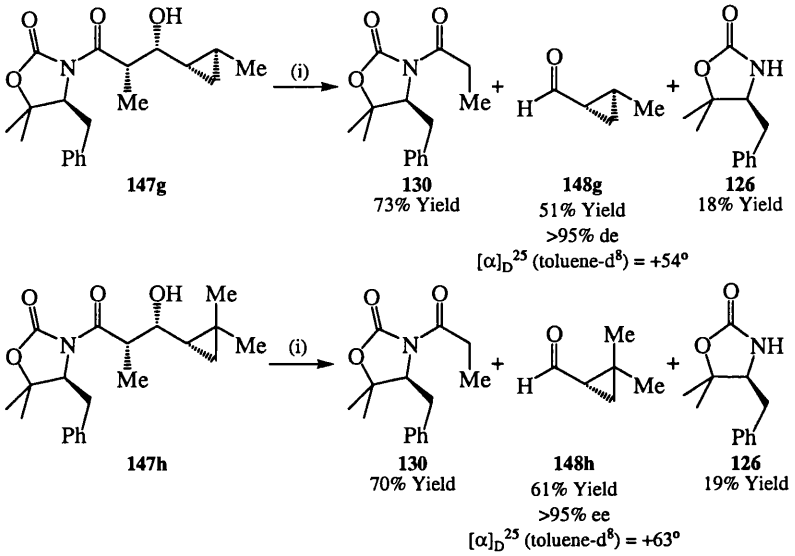
Since epimerisation of the β-stereocentre of cyclopropane carboxaldehydes **148a-148f** was unlikely, each of the cyclopropane carboxaldehydes were assumed to be single enantiomers as determined from their diastereomeric excesses that were found to be >95% de *via* examination of their crude ^{1}H-NMR spectra. No epimerisation at the α-centre of any of the cyclopropane carboxaldehydes was observed, including for *cis*-cyclopropane carboxaldehyde **148f** that had been shown previously to readily epimerise to its more thermodynamically stable *trans*-diastereomer under basic conditions.[109]

Therefore, a series of six cyclopropane carboxaldehydes had been prepared in acceptable to good yields (55% to 75%), and in >95% de in all cases. The absolute configurations of cyclopropane carboxaldehydes **148a** and **148b** were confirmed as (*S*,*S*), *via* comparison of the signs of their specific rotations with literature values previously reported for these chiral aldehydes.[108]

2.2.7 The *retro*-aldol reaction of volatile aldehydes

Attempts to carry out the *retro*-aldol reaction with LiHMDS in toluene on cyclopropyl aldols **147g** and **147h**, failed to afford the desired short chain cyclopropane carboxaldehydes **148g** and **148h**. It was proposed that this failure was probably due to the volatility of these aldehydes that had resulted in their loss during work-up of the reaction due to the need to remove solvent *in vacuo*. To solve this isolation problem, an alternative protocol was devised in which cyclopropyl *syn*-aldols **147g** and **147h** were dissolved in deuterated toluene and LiHMDS (as a 2 mol dm^{-3} solution in toluene-d^8) was added in one portion, followed by stirring for 2 hours at 10°C. The reactions were then quenched with 5 drops of distilled water, dried over

3Å molecular sieves and filtered. The crude reaction mixtures were then distilled under atmospheric pressure (at 120°C for **148g**, and 130°C for **148h**) to afford cyclopropane carboxaldehydes **148g** and **148h** isolated as solutions in toluene-d^8, with overall yields of 65% and 51% respectively (**Scheme 2.2-8**).[110]

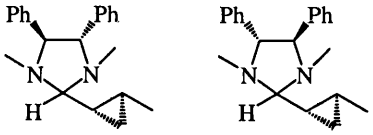


Reagents and conditions: (i) LiHMDS, toluene-d^8, 10°C, 2 hours

Scheme 2.2-8 – *Retro-aldol reaction for the formation of volatile cyclopropane carboxaldehydes*

The yields of cyclopropane carboxaldehydes **148g** and **148h** were calculated by the addition of a known amount of 2,5-dimethylfuran as an internal standard to each distillate. This enabled the concentrations of the cyclopropane carboxaldehyde solutions to be determined accurately by comparing the intensity of their respective integrals in their ^{1}H-NMR spectra. The diastereomeric excess of methyl cyclopropane carboxaldehyde **148g** was determined as greater than 95% by examination of its 300 MHz ^{1}H-NMR spectrum. However, dimethyl cyclopropane carboxaldehyde **148h** contained only a single stereogenic centre at its α-position; therefore, its stereochemical purity could not be determined from analysis of its ^{1}H-NMR spectrum. Mangeney and co-workers have described that the enantiomeric excess of chiral aldehydes can be determined using their chiral diamine derivatising agent that affords imidazolidine diastereomers ideally suited for ^{1}H-NMR spectroscopic

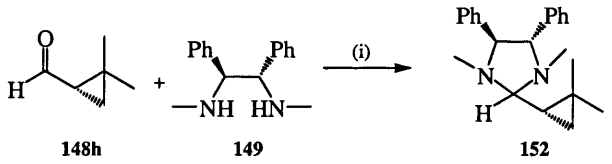
analysis.[111] Barrett and co-workers have previously described the use of this imidazolidine derivatisation approach for determining the enantiomeric excess of methyl cyclopropane **148h** with both enantiomers of chiral diamine **149** being used to prepare diastereomers **150** and **151**.[112] They demonstrated that the two imidazolidine diastereomers **150** and **151** exhibited significantly different ^{1}H-NMR spectra that enable their individual resonances to be clearly distinguished (**Figure 2.2-6**).



150 **151**

Figure 2.2-6 – *Diastereomeric imidazolidines of chiral cyclopropanes*

Therefore, a solution of dimethyl cyclopropane carboxaldehyde **148h** in toluene-d^8, was reacted with enantiopure (1*S*,2*S*)-*N*^{1},*N*^{2}-dimethyl-1,2-diphenylethane-1,2-diamine **149** (**Scheme 2.2-9**) to afford chiral imidazolidine **152**. Examination of the crude 300 MHz ^{1}H-NMR spectrum of this derivatisation reaction revealed a single set of resonances for the peaks corresponding to the imidazolidine fragment of a single diastereomer, and as a consequence the enantiomeric excess of my sample of dimethyl cyclopropane carboxaldehyde **148h** was assumed to be >95% ee.



148h **149** **152**

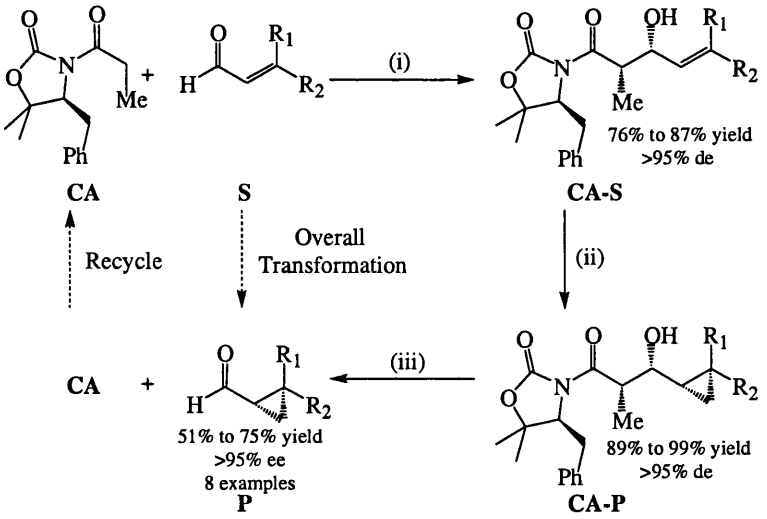
Single diastereomer observed in ^{1}H-NMR spectrum

Reagents and conditions: (i) 4Å MS, Et_2O, 2 hours.

Scheme 2.2-9 – *Derivatisation of dimethyl cyclopropane carboxaldehyde*

2.2.8 Conclusion

Methodology has been developed for the asymmetric synthesis of a series of *N*-propionyl oxazolidin-2-one derived unsaturated aldol substrates **137a** to **137h** in high de and yield. These substrates were cyclopropanated using modified Furukawa's conditions to afford cyclopropyl *syn*-aldols **147a** to **147h** with excellent de in near quantitative yield. The *retro*-aldol reaction of these cyclopropyl *syn*-aldols was then optimised to afford a range of cyclopropane carboxaldehydes with no epimerisation or racemisation of any stereocentres being observed. The original aim of this project had therefore been completed employing temporary stereocentres for asymmetric synthesis in a novel three-step synthesis of chiral cyclopropane carboxaldehydes in 38% to 55% overall yield from the starting chiral auxiliary, and >95% ee in all cases **(Scheme 2.2-10)**.[113]



Reagents and conditions: (i) 9BBN-OTf, $^{i}Pr_2NEt$, CH_2Cl_2, 0°C, 1 hour, α,β-unsaturated aldehyde, -78°C to RT overnight, (ii) Et_2Zn, CH_2I_2, CH_2Cl_2, -10°C to 0°C, 1 to 4 hours; (iii) LHMDS, toluene, 0 to 10°C, 2 hours.

Scheme 2.2-10 – *Novel three-step protocol for the asymmetric synthesis of chiral aldehydes*

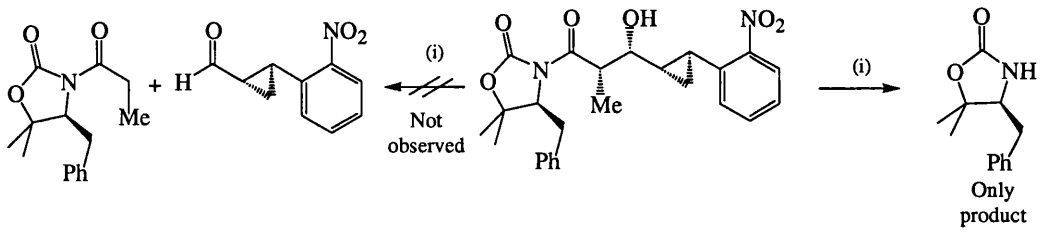
Chapter 2.3 Further developments of the *retro*-aldol reaction and the total synthesis of *Cascarillic acid*

2.3.1 Introduction

This chapter describes further attempts to improve the *retro*-aldol reaction by exploring three alternative synthetic protocols to carry out this critical reaction. Application of optimised *retro*-aldol conditions for the three-step aldol/directed cyclopropanation/*retro*-aldol strategy to a novel total asymmetric synthesis of the cyclopropane containing natural product *Cascarillic acid* is then described.

2.3.2 Proposals for the loss of aldehyde yield

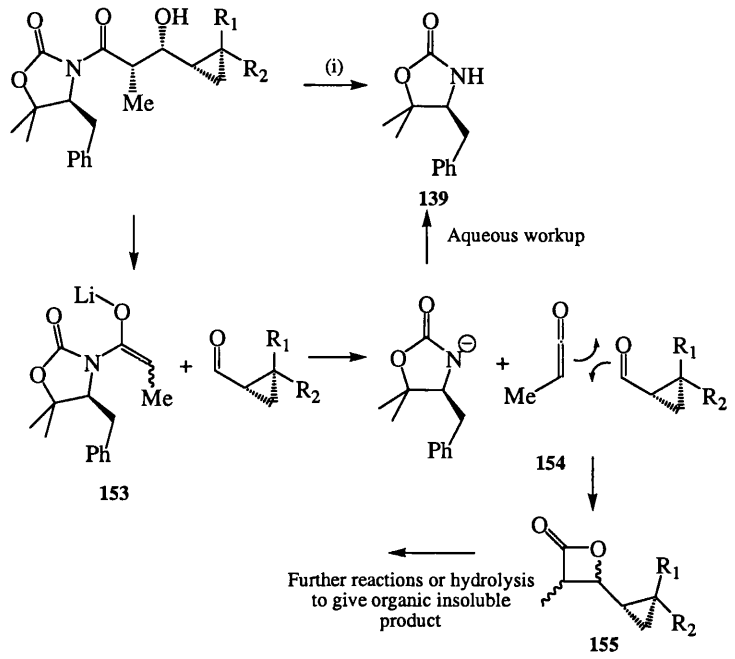
In the previous chapter it was described how competing formation of oxazolidin-2-one **126** as an unwanted side product in the anionic *retro*-aldol reaction of cyclopropyl *syn*-aldols lead to a loss in yield of our desired chiral aldehydes. It was difficult to identify reasons for the loss in yield of aldehyde product in these types of *retro*-aldol reactions, which proved extremely capricious, with different yields of cyclopropane carboxaldehydes being obtained for different types of cyclopropyl aldol substrate under the same conditions. For example, simply changing the temperature of the reaction from 10°C to room temperature in the anionic *retro*-aldol reaction of *syn*-aldol **147d**, resulted in the yield of cyclopropane carboxaldehyde **148d** being reduced from a reasonable 55% yield to almost zero, with the crude ^{1}H-NMR spectra indicating no compounds other than the oxazolidin-2-one auxiliary **126** being present (**Scheme 2.3-1**).



Reagents and conditions:(i) LiHMDS, toluene, RT, 2 hours.

Scheme 2.3-1 – *Loss of aldehyde in the anionic retro-aldol reaction*

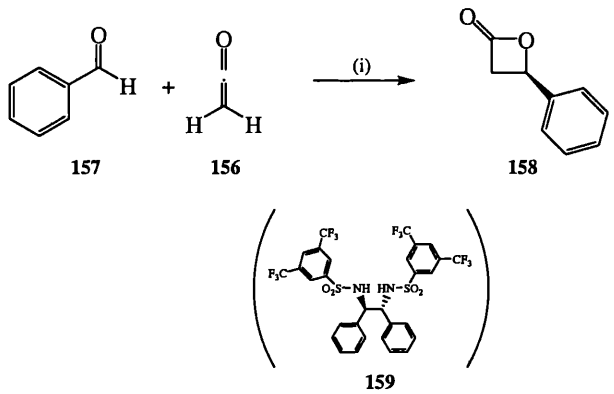
It was therefore proposed that two mechanisms might be operating, whereby the aldehyde fragment could be lost in this reaction. In the first proposed mechanism (**Scheme 2.3-2**), the *retro*-aldol reaction would proceed as desired to afford a cyclopropane carboxaldehyde and lithium enolate **153**. This enolate intermediate would then undergo *retro*-ketene cleavage as previously described (**Scheme 2.1-23**), to afford methyl ketene **154** that could potentially react with the aldehyde in a [2 + 2] cycloaddition reaction, to afford an unstable *beta*-lactone intermediate **155**. This compound could then oligomerise, or be hydrolysed during workup, to afford products that were insoluble in organic solvents. This would therefore leave oxazolidin-2-one **126** as the only observable by-product in the crude ^{1}H-NMR spectrum at the end of the reaction.



Reagents and conditions: (i) LiHMDS, toluene, RT, 2 hours.

Scheme 2.3-2 – *Proposed retro-ketene mechanism for the loss of aldehyde in an anionic retro-aldol reaction*

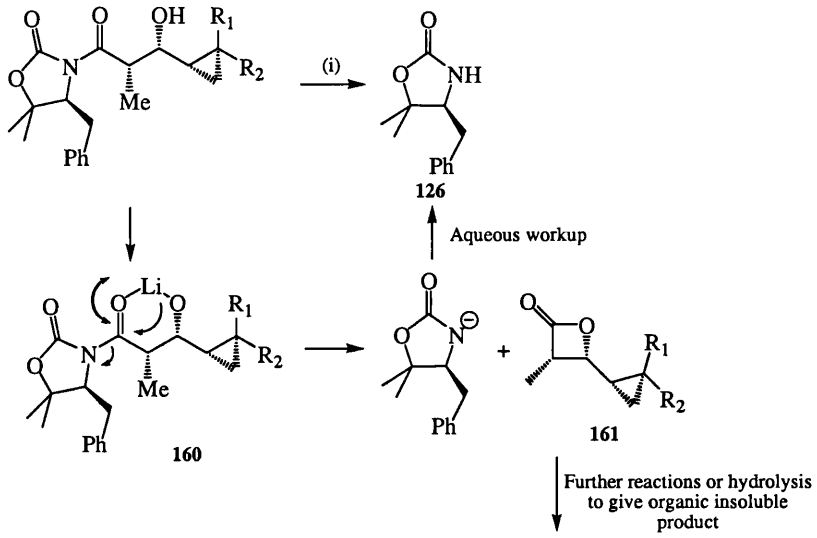
There is literature precedent for this type of pericyclic reaction since Miyano and co-workers have reported a similar asymmetric [2 + 2] cycloaddition reaction of ketene **156** with benzaldehyde **157** in their asymmetric synthesis of chiral β-lactone **158** (**Scheme 2.3-3**).[114]



*Reagents and conditions: Me_3Al, **159**, (10 mol%), Toluene, -78°C.*

Scheme 2.3-3 – *Chiral β-lactone synthesis from aldehydes and ketenes*

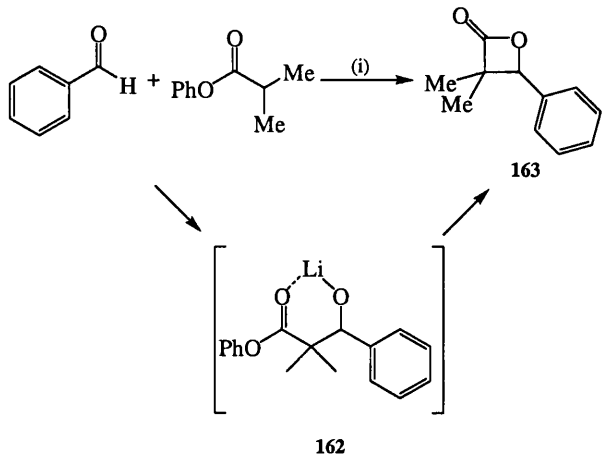
The second mechanism proposed (**Scheme 2.3-4**) would involve lithium alkoxide **160** undergoing competing nucleophilic attack at the exocyclic carbonyl of the aldol substrate, with the anion of oxazolidin-2-one **126** departing as a leaving group. β-Lactone intermediate **161** would then be hydrolysed or oligomerise in a similar manner to afford products that were insoluble in organic solvents, once again leaving oxazolidin-2-one **126** as the only visible by-product in the ^{1}H-NMR spectrum.



Reagents and conditions: (i) LiHMDS, toluene, RT, 2 hours.

Scheme 2.3-4 – *Proposed anionic cyclisation mechanism for the loss of aldehyde yield in the anionic retro-aldol reaction*

Once again there is literature precedent for this reaction pathway since Schick and co-workers proposed a similar cyclisation mechanism in their one pot aldol/β-lactone synthesis, in which a lithium alkoxide intermediate **162** was proposed to cyclise to lactone **163** *in situ* (**Scheme 2.3-5**).[115]



Reagents and conditions: (i) LDA, THF, -78°C.

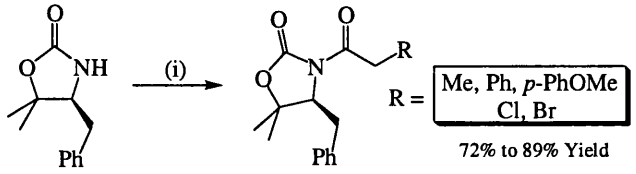
Scheme 2.3-5 – *One pot aldol/β-lactone formation*

Whilst I was unable to identify the causes for the decreased yield in aldehyde formation with any certainty, the optimal conditions established for these *retro*-aldol reactions were consistent with both these mechanisms. Changing the solvent used for the *retro*-aldol reaction from THF to the more aggregating toluene and using lithium as an alkoxide counter-ion instead of potassium was proposed to have stabilised the metal enolate intermediate **153** (or the cyclic metal intermediate **160**), thus limiting the rate of either of these unwanted decomposition pathways and subsequent loss in aldehyde products.

2.3.3 Alternative chiral auxiliaries

Despite completing our three-step step synthesis of chiral aldehydes, we remained frustrated by the precocious nature of the *retro*-aldol reaction that had to be optimised for good yields of individual cyclopropane carboxaldehydes to be achieved. Analysis of each *retro*-aldol reaction had to be carried out by examination by ^{1}H-NMR spectroscopy of the crude reaction mixture following work-up, since monitoring of the reaction by thin-layer chromatography did not accurately reflect the actual products observed in the crude ^{1}H-NMR spectrum.

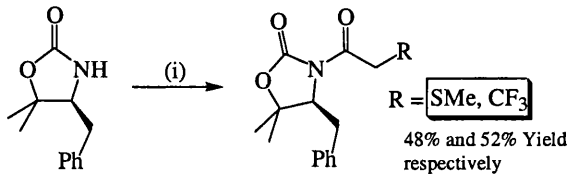
In an attempt to improve the yield of the *retro*-aldol reaction, we decided to screen a range of oxazolidin-2-one chiral auxiliaries that contained different *N*-acetyl substituents. It was proposed that these chiral auxiliaries would afford *syn*-aldol substrates with electron withdrawing groups at their α-positions, which might serve to promote the *retro*-aldol reaction to afford the desired cyclopropane carboxaldehydes in higher yields.[116] Therefore, the lithium anion of oxazolidin-2-one **126** was reacted with five commercially available acid chlorides or bromides to afford *N*-acyl-oxazolidin-2-ones **164** to **167** in 72% to 89% yield, using the previously described procedure (**Scheme 2.3-6**).



Reagents and conditions: (i) ^{n}BuLi, RCH_2COCl or RCH_2COBr, THF, -78 to 0°C.

Scheme 2.3-6 – *Synthesis of various N-acylated oxazolidin-2-one auxiliaries using commercially available acid chlorides and bromides*

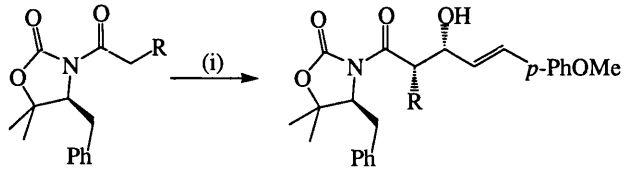
Two further *N*-acylated oxazolidin-2-ones **168** and **169** were synthesised *via* an alternative procedure, where their corresponding commercially available acids were converted *in-situ* to their acid chlorides using oxalyl chloride and triethylamine in the presence of a catalytic amount of DMF. The resultant acid chlorides were then reacted with the lithium anion of the oxazolidin-2-one **126** in the usual manner (**Scheme 2.3-7**).[117]



Reagents and conditions: (i) Oxalyl chloride, RCH_2CO_2H, 5 mol% DMF, THF, 0°C, 1 hour, then ^{n}BuLi, oxazolidin-2-one, THF, -78 to 0°C, THF, 2 hours.

Scheme 2.3-7 – *Synthesis of N-acylated oxazolidin-2-ones from commercially available acids*

The boron enolates of these new chiral auxiliaries were then reacted with *para*-methoxycinnamaldehyde under our standard *syn*-aldol conditions (9BBN-OTf, $^{i}Pr_2NEt$) to afford *syn*-aldols **164** to **169** in moderate to good de (59 to >95% de). The results of these aldol reactions are summarised in **Table 2.3-1**.



Entry	*R*	*Auxiliary*	*Aldol*	*Conv.*[a]	*de*[a]
1	Me	**130**	**137c**	90	>95
2	Ph	**164**	**164a**	78	90
3	*p*-PhOMe	**165**	**165a**	70	73
4	Cl	**166**	**166a**	81	81
5	Br	**167**	**167a**	65	63
6	SMe	**168**	**168a**	63	59
7	CF_3	**169**	**169a**	0	/

Reagents and conditions: (i) 9BBN-OTf, $^{i}Pr_2NEt$, CH_2Cl_2, 0°C, 1 hour, (E)-para-methoxycinnamaldehyde, -78 to RT, overnight; (a) de determined by examination of the crude 300 MHz ^{1}H-NMR spectrum.

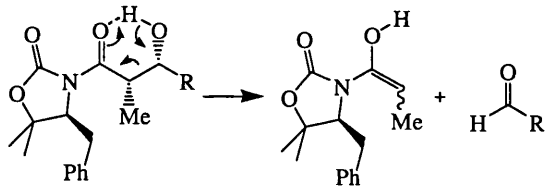
Table 2.3-1 – *Asymmetric syn-aldol reaction of various N-acylated oxazolidin-2-one auxiliaries*

It was immediately apparent that the levels of stereocontrol observed in these aldol reactions were inferior to the very high levels (>95% de) originally obtained in the *syn*-aldol reaction of *N*-propionyl-oxazolidin-2-one **130** (**Entry 1**). The *syn*-aldol reaction of α-phenylacetyl-oxazolidin-2-one **164** (**Entry 2**) afforded *syn*-aldol **164a** in an acceptable 90% de, but the compound proved unstable to purification by silica-gel chromatography. The α-*para*-methoxyphenylacetyl-oxazolidin-2-one derived aldol **165a** (**Entry 3**) was stable to chromatography; however, the diastereomeric excess of 73% was low and the major diastereomeric aldol products could not be separated. α-Halo oxazolidin-2-ones **166** and **167** (**Entries 4 and 5**) displayed a similar drop in diastereoselective control (63-81% de); whilst, α-thio oxazolidin-2-one **168** (**Entry 6**) displayed the lowest selectivity of 59% de. Interestingly, α-

trifluoromethylacetyl-oxazolidin-2-one **169** (**Entry 7**) gave no *syn*-aldol product at all resulting in only unreacted α-trifluoromethylacetyl-oxazolidin-2-one **169** being recovered at the end of the reaction. Therefore, due to the relatively poor diastereocontrol observed for these chiral auxiliaries in the asymmetric *syn*-aldol reaction, these aldol products were not carried further through our three-step protocol.

2.3.4 Pyrolysis of *syn*-aldol substrates: High temperature thermal *retro*-aldol reactions

Disappointed by our attempts to change the α-substituent of the chiral auxiliary as a strategy to promote the *retro*-aldol reaction, it was decided to examine alternative methodologies to develop an improved *retro*-aldol reaction using *N*-propionyl-oxazolidin-2-one chiral auxiliary **130**. Intuitively, the *retro*-aldol reaction may be achieved by simple hydrogen transfer from the β-hydroxyl substituent to the exocyclic carbonyl of the *syn*-aldol substrate **170** in a *pseudo*-pericyclic process to afford an enol **171** and an aldehyde (**Scheme 2.3-8**).

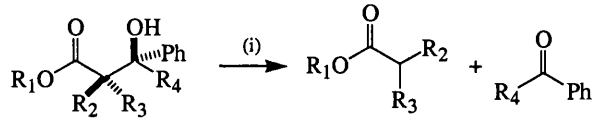


170 **171**

Scheme 2.3-8 – *Proposed thermal retro-aldol reaction*

This type of pericyclic rearrangement reaction has been shown to occur for β-hydroxyesters at 170°C by Houminer and co-workers (**Table 2.3-2**). [118] They demonstrated that increasing the steric demand of the α- and β-substituents of the aldol substrate dramatically increased the rate of decomposition and therefore concluded that the reaction was proceeding through a cyclic intramolecular hydrogen

bonded transition state, such that the driving force for this thermal *retro*-aldol reaction was as a result of the release of steric strain from a chair-like transition state.

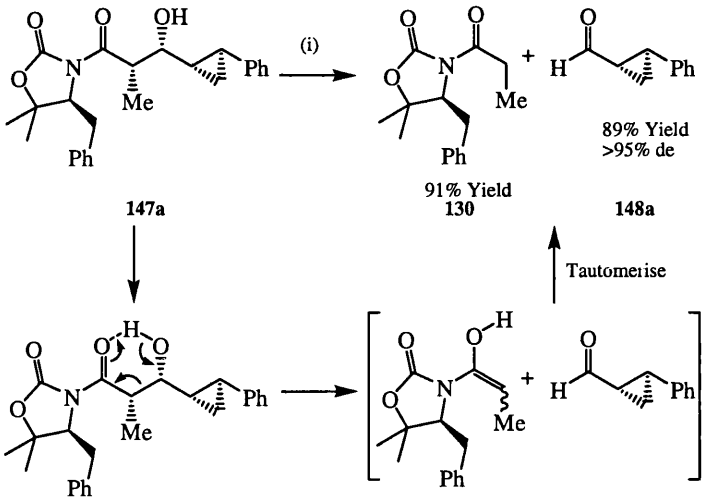


Entry	R_1	R_2	R_3	R_4	*Exper.* k_Δ *(rel.)*
1	Me	H	H	H	1
2	Me	Me	Me	H	20
3	Et	H	^{i}Pr	Me	96
4	Me	Me	Me	Me	2100

Reagents and conditions: (i) 170°C, diglyme.

Table 2.3-2 – *Pyrolysis of β-hydroxyesters*

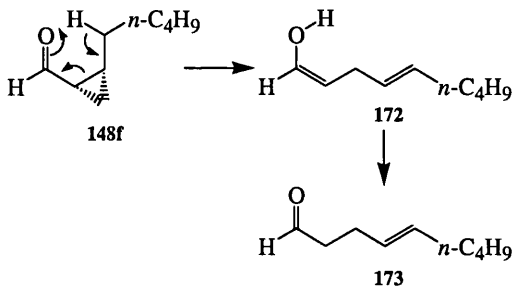
It was proposed that these thermal conditions for the *retro*-aldol reaction might be applicable to our α-methyl cyclopropyl *syn*-aldol substrates. Therefore, neat α-methyl cyclopropyl *syn*-aldol **147a** was heated in a Kugelrohr under reduced pressure (400 mb) in the absence of solvent. At 220°C, phenyl cyclopropane carboxaldehyde **148a** was observed to distil from the reaction bulb to give spectroscopically pure material. Upon completion of this distillation, the residual product that remained in the reaction bulb was found to be spectroscopically pure *N*-propionyl-oxazolidin-2-one **130**, with no decomposition to the parent oxazolidin-2-one **126** being observed. It was therefore concluded that coordination of the β-hydroxy functionality to the exocyclic carbonyl of the aldol fragment had initiated the desired *pseudo*-pericyclic reaction, resulting in clean *retro*-aldol cleavage of *syn*-aldol **147a** (**Scheme 2.3-9**).[119]



Reagents and conditions: (i) 220°C.

Scheme 2.3-9 – *Pyrolysis of α-methyl phenyl cyclopropyl syn-aldol 147a*

Unfortunately, it was found that this type of thermal *retro*-aldol reaction was limited to the synthesis of cyclopropane carboxaldehydes that did not contain γ-protons prone to elimination, since heating *cis*-cyclopropyl *syn*-aldol **147f** to 220°C resulted in the formation of two aldehyde products that were inseparable by chromatography. Examination of the ^{1}H-NMR spectrum (see **Appendix 4.2**) of the crude reaction product revealed the expected cyclopropane carboxaldehyde **148f** (CHO doublet at δ9.35 ppm), and a second aldehyde peak at δ9.72 ppm that appeared as a triplet. Since this crude ^{1}H-NMR spectrum also revealed a 2H multiplet at δ5.31 ppm, characteristic of a non-conjugated alkene group, it was tentatively concluded that cyclopropane carboxaldehyde **148f** had undergone a further *pseudo*-pericyclic elimination reaction of the cyclopropane ring to afford acyclic aldehyde **173** (**Scheme 2.3-10**).

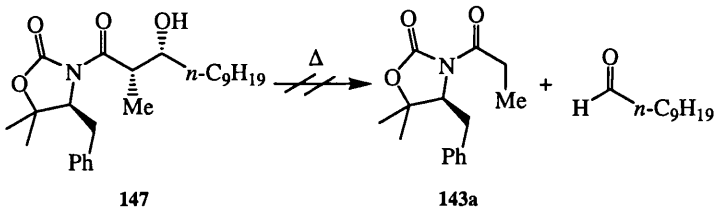


Scheme 2.3-10 – *Proposed mechanism for the pseudo-pericyclic decomposition of cis-cyclopropane carboxaldehyde **148f***

Due to the orientation of the *cis*-cyclopropane ring in aldehyde **148f**, the C3-C4 bond can easily rotate to adopt a conformer that positions the allylic carbon-hydrogen bond close to the aldehyde carbonyl, thus affording a six-membered transition state. This hydrogen atom is then transferred to the aldehyde carbonyl, resulting in cleavage of the cyclopropane ring to afford enol intermediate **172**, which then simply tautomerises to afford *bis*-homoallylic aldehyde **173**.[120]

Despite repeated attempts, I was unable to devise distillation conditions that would remove cyclopropane carboxaldehyde **148f** from the Kugelrohr bulb quickly enough to prevent this second rearrangement reaction from occurring. Similar elimination products were observed in the thermal *retro*-aldol reaction that afforded dimethyl cyclopropane carboxaldehyde **148h**.

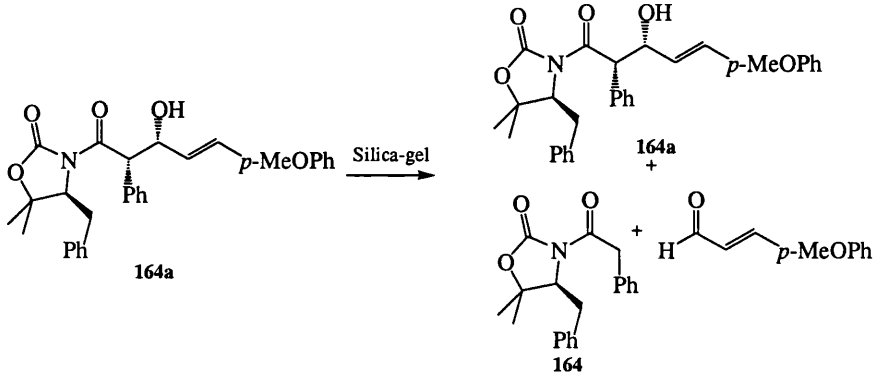
Finally, it should be noted that attempts to carry out this thermal *retro*-aldol reaction on saturated acyclic *syn*-aldol **134** that does not contain a cyclopropane ring proved unsuccessful, even at temperatures above 250°C. This indicated that the presence of the cyclopropane motif within the *syn*-aldol was essential for successful pyrolysis of these compounds, presumably due to the added release of steric strain in the trasition state that results from the presence of the cyclopropane ring (**Scheme 2.3-11**).



Scheme 2.3-11 – *Failed pyrolysis of non-cyclopropyl syn-aldol **134***

2.3.5 Pyrolysis of *syn*-aldol substrates: Surface catalysed thermal *retro*-aldol reactions

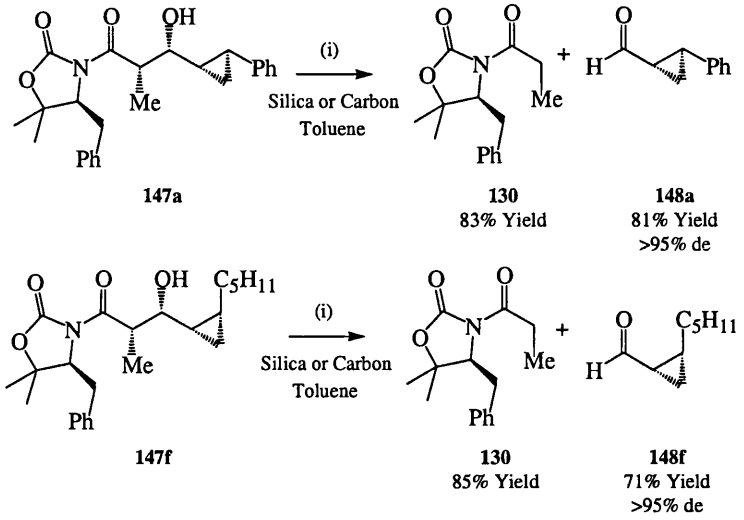
It was proposed that the high temperatures required for the thermal *retro*-aldol reaction of relatively simple aldol substrates were unlikely to be applicable to more structurally complex substrates containing sensitive functionality. Furthermore, it was anticipated that if the temperature at which the pyrolysis reaction occurred could be reduced, then competing cyclopropane ring cleavage might be avoided. It had been previously observed that the attempted purification of α-phenyl *syn*-aldol product **164a** *via* silica-gel chromatography had resulted in partial *retro*-aldol decomposition (**Scheme 2.3-12**) and as a consequence, we wondered whether we this observation could be exploited to lower the temperature of the thermal *retro*-aldol reaction.



Scheme 2.3-12 – *Partial retro-aldol decomposition of syn-aldol **164a** over silica-gel*

Firstly, it was found that refluxing α-methyl cyclopropyl *syn*-aldol **147a** in toluene for twelve hours resulted in no *retro*-aldol reaction, with only starting material being recovered in quantitative yield. Addition of 10 mol% silica (or activated carbon) to the reaction mixture in refluxing toluene, resulted in complete *retro*-aldol cleavage after 6 hours to afford cyclopropane carboxaldehyde **148a** in 81% yield and >95% de. *Retro*-aldol cleavage of α-methyl *cis*-cyclopropyl *syn*-aldol **147f** was also complete after eight hours under these conditions, with no evidence of any products arising from competing cleavage of the cyclopropane ring. Therefore, the presence of a

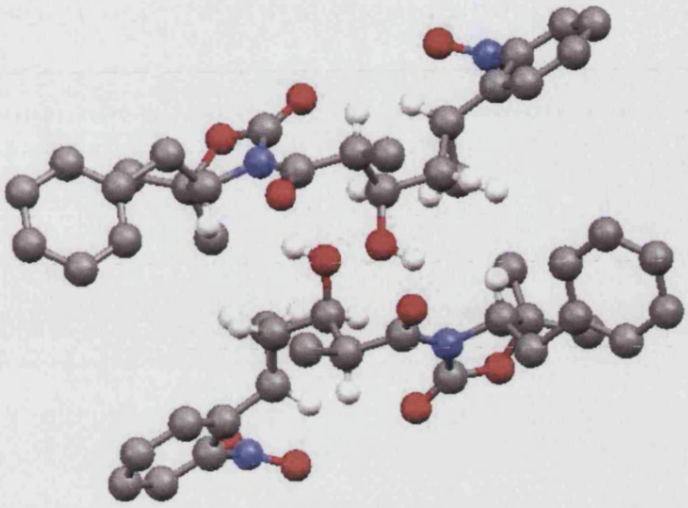
heterogeneous solid capable of adsorbing the aldol substrate onto its surface had reduced the pyrolysis activation temperature for these aldol substrates by over 100°C.



Reagents and conditions:(i) 10 mol% silica or activated carbon, toluene, 110°C, 6 hours.

Scheme 2.3-13 – *Surface catalysed pyrolysis of α-methyl cyclopropyl syn-aldols*

It was proposed that the mechanism of this surface catalysed *retro*-aldol reaction was likely to be due to a 'templation' effect that promotes an intramolecular hydrogen bond within the cyclopropyl aldol substrate by adsorption to the surface. Examination of the solid state X-ray crystal structure of α-methyl *o*-nitrophenyl cyclopropyl *syn*-aldol **147d** revealed that the hydrogen atom of its hydroxyl functionality is directed *away* from the exocyclic carbonyl, to form an intermolecular hydrogen bond in the solid state, such that a herring bone motif is formed throughout the crystal (**Figure 2.3-1**).

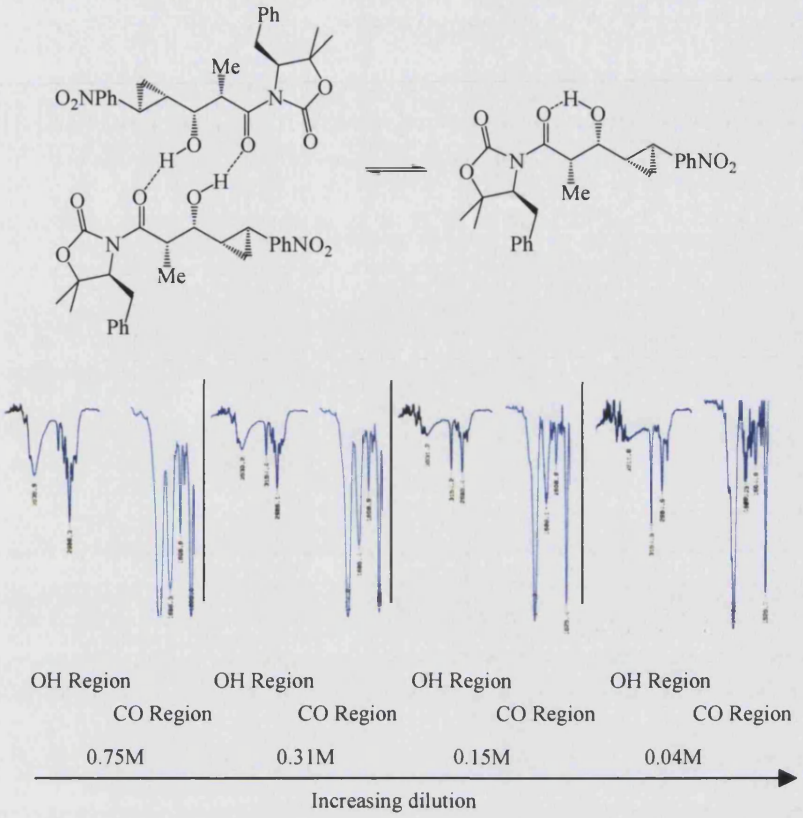


Selected hydrogens omitted for clarity; Red = Oxygen, Grey = Carbon, Purple = Nitrogen, White = Hydrogen.

Exocyclic carbonyl – Hydroxyl oxygen: Hydrogen Bond length = 2.774(3) Å; Exocyclic carbonyl – Hydroxyl hydrogen: Hydrogen Bond length = 2.286 Å;O-H-O angle = 117.86(16)°.

Figure 2.3-1 – *X-ray crystal structure of syn-aldol **147d** displaying an intermolecular hydrogen bond*

This intermolecular conformational ground state clearly suggests an intrinsic energy barrier to the formation of an intramolecular six-membered transition state conformation that is required for the thermal *retro*-aldol reaction. To reveal whether this intermolecular hydrogen bond was also prevalent in solution state, we carried out infrared spectroscopic analysis of α-methyl *o*-nitrophenyl cyclopropyl *syn*-aldol **147d** dissolved in chloroform at various concentrations (**Scheme 2.3-14**).



Scheme 2.3-14 – *Infra-red spectroscopic analysis of different concentrations cyclopropyl syn-aldol in chloroform*

It was found that the oxazolidin-2-one carbonyl stretch appeared at 1774 cm^{-1} and remained constant throughout the change in concentration, indicating that it is not involved in any hydrogen bonding interaction. At high concentrations (0.75 mol dm^{-3}) the exocyclic carbonyl displays a single ν(C=O) stretch at 1686 cm^{-1}, with the hydroxyl group displaying a broad intermolecular hydrogen bond absorption at 3536 cm^{-1}. Halving the concentration to 0.31 mol dm^{-3} resulted in the exocyclic carbonyl and hydroxyl absorptions decreasing in intensity with respect to that of the oxazolidin-2-one carbonyl. When the concentration was halved again to 0.15 mol dm^{-3}, the sharp absorption at 3154 cm^{-1} increased in intensity, whilst the exocyclic carbonyl had resolved itself into two absorptions at 1686 and 1677 cm^{-1} (**Figure 2.3-2**).

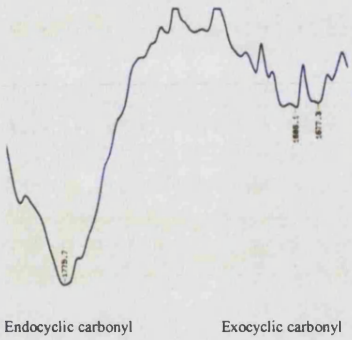


Figure 2.3-2 – *Expanded carbonyl region of IR-spectrum displaying splitting of the exocyclic carbonyl absorptions*

Finally, at low concentrations (0.04 mol dm^{-3}) the new absorption at 3154 cm^{-1} became increasingly strong, the broad absorption at 3536 cm-1 had essentially disappeared, whilst the exocyclic carbonyl region had split cleanly into two distinct absorptions at 1686 cm^{-1} and 1677 cm^{-1}.

This infrared analysis was interpreted to infer that at high concentrations, the cyclopropyl aldol exists almost exclusively as a hydrogen bond dimer, therefore displaying only a single set of absorptions. As the solution becomes increasingly dilute, the molecule becomes less likely to form this dimer and intramolecular hydrogen bonding begins to occur, which results in an increase in intensity of the sharp absorption band for intramolecular hydrogen bonding at 3154 cm^{-1}, and splitting of the exocyclic carbonyl absorption into two peaks at 1686 cm^{-1} and 1677 cm^{-1}.[121]

With reference to the thermal *retro*-aldol reaction previously described, it is proposed that adsorption of the aldol substrate onto a surface shifts the position of equilibrium from the hydrogen-bonded dimer to the monomeric species, which in turn is responsible for the *retro*-aldol reaction.

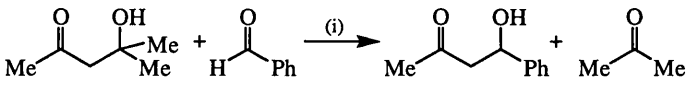
This proposed mechanism is likely to be an oversimplification of the reaction pathway occurring in the thermal *retro*-aldol reaction; however, it is clear that an 'activated' surface is certainly required for the *retro*-aldol reaction of these types of aldol substrate to occur at lower temperatures. Interestingly, attempts to carry out the

thermal *retro*-aldol reaction under stringently dry conditions, or by adding triethylamine to the reaction mixture prevented the *retro*-aldol reaction from occurring.

In conclusion, although this thermal *retro*-aldol reaction provides a useful addition to our list of fragmentation conditions, it also proved to be quite inconsistent, sometimes failing to produce the same results under identical conditions, and it therefore requires further optimisation if it is to prove to be synthetically versatile alternative.

2.3.6 Samarium(II) iodide, a unique reagent for the *retro*-aldol reaction

Recent work by Nevalainen and Simpura demonstrated that treatment of β-hydroxy ketones with trimethyl aluminium derivative in the presence of benzaldehyde resulted in a *trans*-aldol reaction occurring to afford a new aldol product **174** and acetone (**Scheme 2.3-15**).[122]



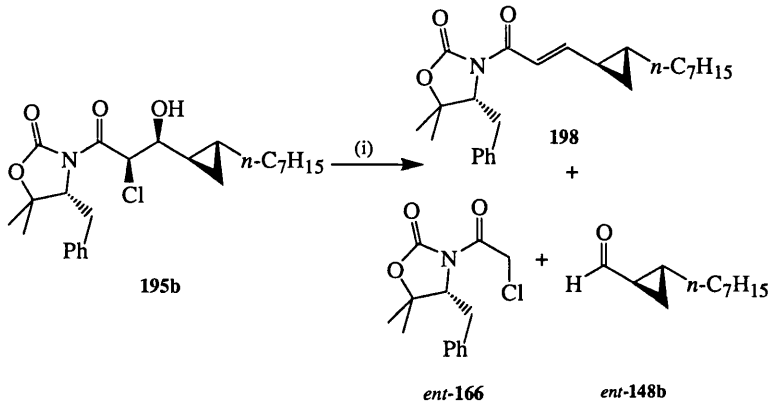
174

Reagents and conditions: (i) BINOL-AlMe (5 mol%), CH_2Cl_2, 48 hours.

Scheme 2.3-15 – *Lewis acid mediated aldol transfer reaction*

Attempts to repeat this reaction using our cyclopropyl aldol substrates with trimethyl aluminium and lanthanum triiodide[123] in the absence of any sacrificial aldehyde, failed to initiate a *retro*-aldol reaction, affording only unreacted starting aldol. However, during concurrent studies into the synthesis of *Grenadamide* (discussed in **Chapter 2.4.5**), we observed that attempts to carry out a samarium(II) iodide mediated elimination reaction of α-chloro-β-hydroxy *syn*-aldol **195b**, resulted in an unexpected *retro*-aldol reaction (**Scheme 2.3-16**). Therefore, it was found that

treatment of *syn*-aldol **195b** with two equivalents of samarium(II) iodide produced the desired elimination product **198** in only 60% yield, with *N*-chloroacetyl-oxazolidin-2-one ***ent*-166** and cyclopropane carboxaldehyde ***ent*-150c** being observed as competing side products.

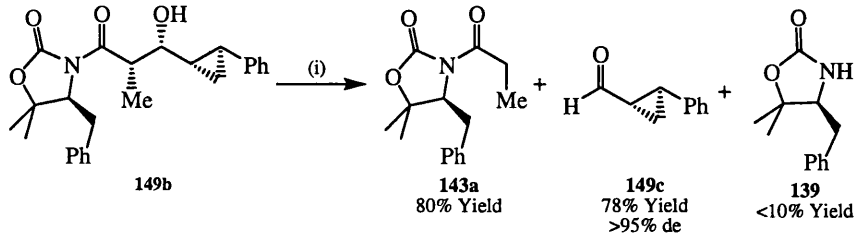


Reagents and conditions: (i) SmI_2 (2 eq.), THF, RT, 2 hours

Scheme 2.3-16 – *Retro-aldol reaction in the synthesis of Grenadamide*

Since this *retro*-aldol reaction had occurred in the presence of competition from the β-elimination reaction, it was proposed that treatment of an α-methyl cyclopropyl *syn*-aldol substrate that was not susceptible to β-elimination should result in a clean *retro*-aldol cleavage.

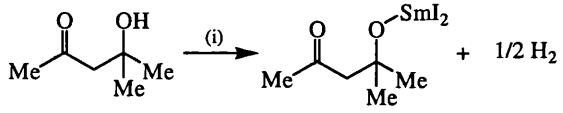
Therefore, it was established that treatment of α-methyl cyclopropyl *syn*-aldol **147a** with two equivalents of samarium(II) iodide at room temperature resulted in a clean *retro*-aldol reaction to afford the desired cyclopropane carboxaldehyde **148a** in 78% yield and >95% de, with less than 10% yield of the parent oxazolidin-2-one **126** being observed (**Scheme 2.3-16**).



Reagents and condition; (i) SmI_2 (2.5 eq.), THF, RT, 2 hours.

Scheme 2.3-17 – *Samarium(II) iodide mediated retro-aldol reaction of α-methyl cyclopropyl syn-aldol **147a***

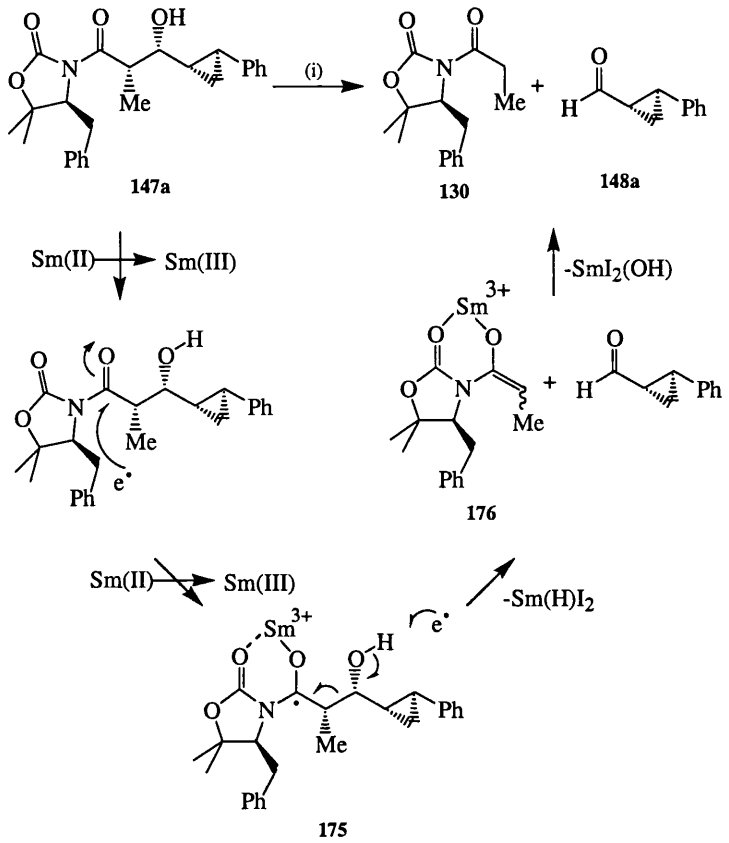
The mechanism of this novel *retro*-aldol reaction was not easily explained. Collin and co-workers have previously used samarium(II) iodide as an Oppenauer oxidation catalyst and implied the formation of a samarium(III) alkoxide species derived from aldol substrates, but this reaction also required the presence of nickel(II) bromide as a catalyst to proceed (**Scheme 2.3-18**).[124]



Reagents and conditions: (i) SmI_2 (2 eq.), $NiBr_2$, THF, 30 minutes.

Scheme 2.3-18 – *Samarium alkoxide formation from aldol substrates*

No co-catalyst was required for our samarium(II) iodide mediated *retro*-aldol reaction, but it was evident that the reaction did require two equivalents of reagent to proceed to completion. Samarium(II) iodide is known to be a strong single electron donor, and during the reaction a gradual colour change was observed from the deep blue of a samarium(II) species, to the characteristic yellow colour of a samarium(III) species. Therefore, it was tentatively proposed that the following mechanism is operating for the samarium(II) mediated *retro*-aldol reaction of our aldol substrates (**Scheme 2.3-19**).



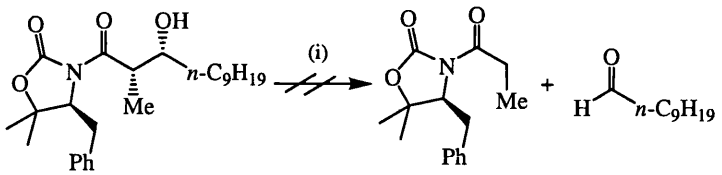
Reagents and conditions: (i) SmI_2 (2.5 equ.), THF, RT, 2 hours.

Scheme 2.3-19 – *Proposed mechanism for the samarium(II) mediated retro-aldol reaction*

Oxidation of samarium(II) to samarium(III) releases an electron, which reduces the exocyclic carbonyl of *syn*-aldol **147a**, to afford samarium(III) radical enolate intermediate **175**. Oxidation of a second equivalent of samarium(II) to samarium(III) releases a second electron that abstracts the β-hydroxyl proton, thus initiating a radical mediated *retro*-aldol reaction,[125] to afford phenyl cyclopropane carboxaldehyde **148a** and samarium(III) enolate **176**, which is subsequently protonated to afford *N*-propionyl oxazolidin-2-one **130**. It is proposed that the radical recombination step for the elimination of **175** provides the driving force for the homolytic cleavage of its O-H bond, which is normally considered to be an unfavourable process.

In contrast, saturated *syn*-aldol **134** displayed no *retro*-aldol cleavage when reacted with two equivalents of samarium(II) iodide under identical conditions (**Scheme**

2.3-20), indicating once again that release of steric strain plays a pivotal role as the driving force in *retro*-aldol reaction of these types of *syn*-aldol substrates.



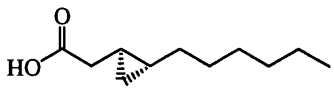
147 **143a**

Reagents and conditions: (i) SmI_2, THF, RT, 2 hours.

Scheme 2.3-20 – *Failed samarium(II) mediated retro-aldol reaction of saturated aldol **134***

2.3.7 Applying our three-step synthesis of cyclopropane carboxaldehydes: a previous total synthesis of *Cascarillic acid*

In the previous chapter it was described how a novel three-step aldol/directed cyclopropanation/*retro*-aldol strategy was used for the asymmetric synthesis of cyclopropane carboxaldehydes in high yield. Following a review of the literature, it was decided to apply this methodology to the asymmetric synthesis of the cyclopropane containing natural product *Cascarillic acid* **177** (**Figure 2.3-3**). It was also intended that this synthesis would also serve as a real test for our optimised *retro*-aldol conditions.

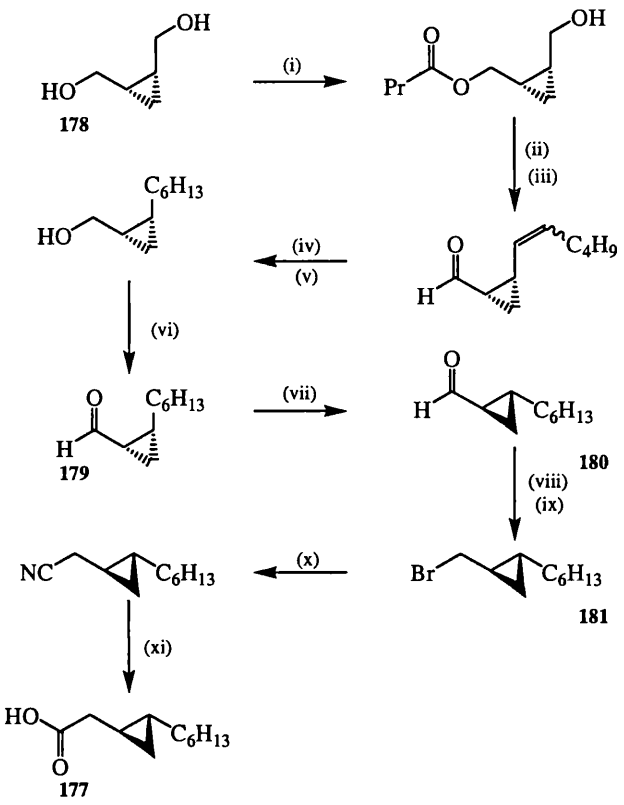


177

Figure 2.3-3 – *Cascarillic acid **177***

Cascarillic acid **177** is a major component of cascarilla essential oil that has been used for many years in the treatment of colds and bronchitis.[126] It has an interesting structure that contains a *trans*-cyclopropane ring in its fatty acid chain, which is in contrast to the majority of naturally occurring cyclopropane fatty acids that are *cis* in orientation.[127] Baird and co-workers recently confirmed the absolute stereochemistry

of this compound to be 2-((1*S*,2*R*)-2-hexylcyclopropyl)acetic acid **177** through its total synthesis from *meso-cis*-1,2-dihydroxymethylcyclopropane **178** (**Scheme 2.3-21**).[128]

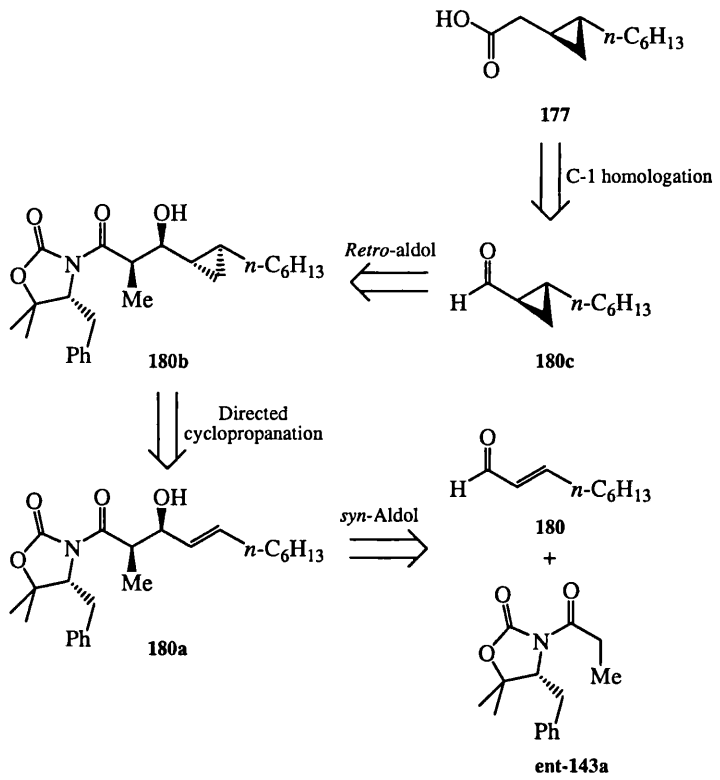


Reagents and conditions: (i) Trifluoroethyl butyrate, lipase, (ii) PCC, CH_2Cl_2, (iii) $Br^-P^+Ph_3(CH_2)_4Me$, BuLi, THF –40°C, (iv) $LiAlH_4$, THF, (v) N_2H_4, H_2O, $NaIO_4$, CH_3COOH, $CuSO_4$, (vi) PCC, CH_2Cl_2, (vii) NaOMe, MeOH, (viii) $LiAlH_4$, THF, (ix) 1,2-bis-diphenylphosphinoethane, Br_2, CH_2Cl_2, (x) NaCN, DMSO, (xi) NaOH, H_2O, EtOH.

Scheme 2.3-21 – *Baird's total synthesis of Cascarillic acid*

Baird's synthesis of *Cascarillic acid* **177** comprised eleven linear steps, including enzymatic desymmetrisation of *meso-cis*-1,2-dihydroxymethylcyclopropane **178**, epimerisation of *cis*-(1*S*,2*R*)-2-hexylcyclopropanecarbaldehyde **179** to its more thermodynamically stable *trans*-(1*R*,2*R*)-2-hexylcyclopropanecarbaldehyde diastereomer **180c**, and a one-carbon homologation of bromide **181** to afford carboxylic acid **177** using sodium cyanide. We believed that this was an overly long and complicated synthesis for such a simple natural product that contained only two

stereocentres and therefore devised an alternative total synthesis of *Cascarillic acid* according to the *retro*-synthetic analysis shown in **Scheme 2.3-22**.

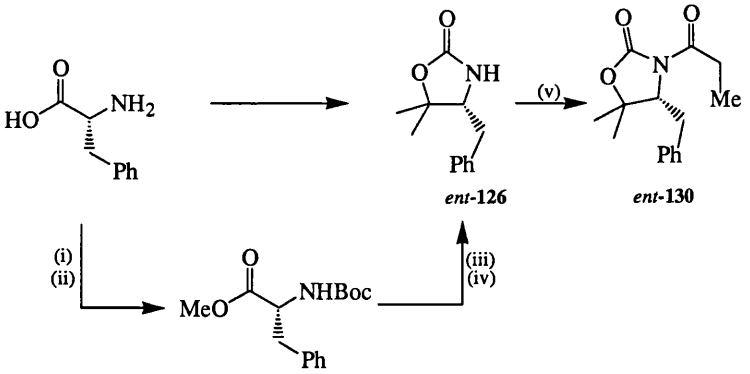


Scheme 2.3-22 – *Retro-synthetic analysis of Cascarillic acid*

In this new *retro*-synthetic analysis of *Cascarillic acid*, there are two key transformations. Firstly, the one carbon homologation of **180c** to **177** would be achieved using dithiane anion/Peterson elimination methodology first established by Corey *et al*,[129] thus eliminating the need to use toxic cyanide chemistry. Secondly, we would use our new three-step synthesis of cyclopropane carboxaldehydes to generate the key aldehyde intermediate **180c** with defined absolute and relative stereochemistry. This reaction sequence would therefore generate *Cascarillic acid* in only five steps from chiral auxiliary *ent*-**130**, thus allowing easy access to structural analogues of this natural product by simply varying the α,β-unsaturated aldehyde substrate used in the initial *syn*-aldol reaction.

2.3.8 Asymmetric synthesis of the key cyclopropane carboxaldehyde intermediate

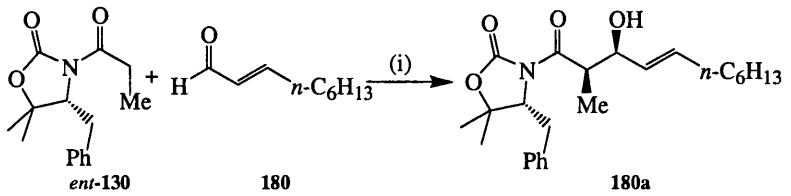
The *N*-propionyl oxazolidin-2-one auxiliary ***ent*-130** was prepared from unnatural (*R*)-phenylalanine according to the procedure described earlier in this thesis. It was necessary to use the (*R*)-enantiomer of the SuperQuat oxazolidin-2-one to generate the correct absolute stereochemistry of the key cyclopropane carboxaldehyde intermediate **180c** (**Scheme 2.3-23**).



Reagents and conditions: (i) $SOCl_2$, MeOH, 12 hours; (ii) Boc-anhydride, $NaHCO_3$, EtOH, 48 hours; (iii) Mg, CH_3I, THF, 48 hours; (iv) KO^tBu, THF, 2 hours; (v) ^nBuLi, propionyl chloride, THF, -78 to 0°C, 2 hours.

Scheme 2.3-23 – *Synthesis of (R)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one*

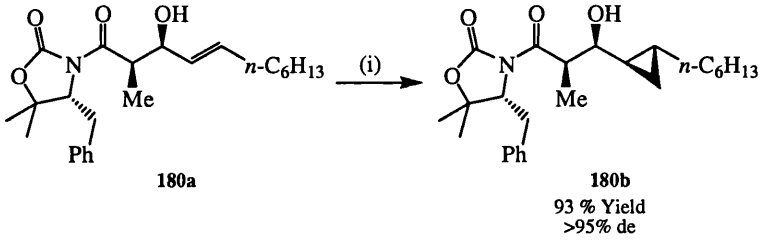
The (*R*)-*N*-propionyl oxazolidin-2-one auxiliary ***ent*-130** was then reacted with (*E*)-non-2-enal under our standard *syn*-aldol conditions (9BBN-OTf, $^iPr_2NEt$), to afford unsaturated aldol intermediate **180a** in >95% de as determined by examination of the crude 300 MHz ^{1}H-NMR spectrum, and in 82% yield after purification by silica gel chromatography (**Scheme 2.3-24**). The *syn*-stereochemistry was assigned as shown from literature precedent and confirmed by the small coupling constant of the α-proton of $J_{2,3}$ = 4.0 Hz.



Reagents and conditions: (i) 9BBN-OTf, $^{i}Pr_2NEt$, CH_2Cl_2, 0°C, 1 hour, (E)-non-2-enal, -78°C to RT overnight.

Scheme 2.3-24 – *Asymmetric syn-aldol reaction of non-2-enal*

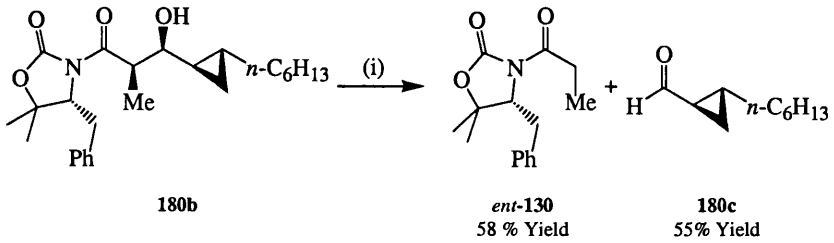
β-vinyl *syn*-aldol intermediate **180a** was then cyclopropanated under our standard Charette conditions to give cyclopropyl aldol intermediate **180b** in >95% de from examination of the crude 300 MHz ^{1}H-NMR spectrum and in 93% yield following purification by silica gel chromatography (**Scheme 2.3-25**).



Reagents and conditions: (i) Et_2Zn, CH_2I_2, CH_2Cl_2, -10 to 0°C, 2 hours.

Scheme 2.3-25 – *Directed cyclopropanation of syn-aldol 180a*

Cyclopropyl *syn*-aldol **180b** was then treated with LiHMDS in toluene; however, despite repeated attempts to optimise this *retro*-aldol reaction (**Scheme 2.3-26**), we were only able to achieve a 55% yield of the key (1*R*,2*R*)-2-hexylcyclopropanecarbaldehyde **180c**.[130]

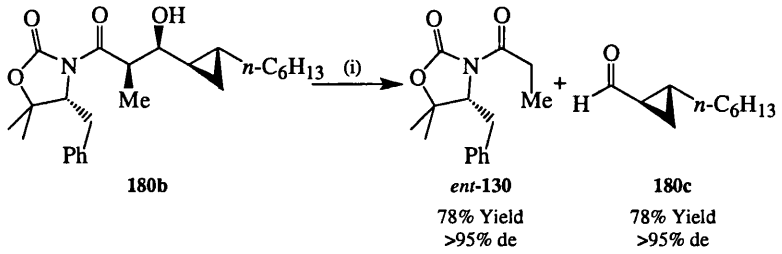


180b | ***ent*-130** 58 % Yield | **180c** 55% Yield

Reagents and conditions: (i) LHMDS, toluene, 10°C, 2 hours.

Scheme 2.3-26 – *Retro-aldol reaction of cyclopropyl syn-aldol **180b***

Consequently, our novel samarium(II) iodide mediated *retro*-aldol reaction methodology was applied to the synthesis of key cyclopropane carboxaldehyde intermediate **180c**. α-methyl cyclopropyl *syn*-aldol **180b** was treated with two equivalents of samarium(II) iodide in THF, to afford the desired cyclopropane carboxaldehyde **180c** in an improved 78% yield (**Scheme 2.3-27**).



180b | ***ent*-130** 78% Yield >95% de | **180c** 78% Yield >95% de

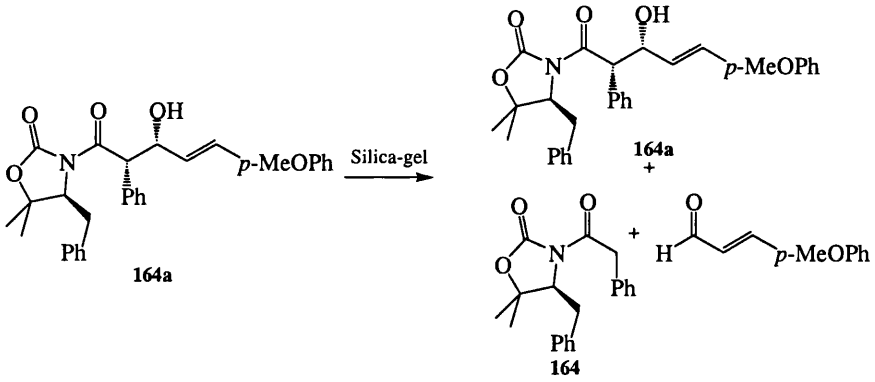
Reagents and conditions: (i) SmI_2 (2 eq.), THF, RT, 2 hours.

Scheme 2.3-27 – *Samarium(II) iodide mediated retro-aldol reaction in the synthesis of Cascarillic acid*

Despite this improvement in yield, samarium(II) iodide proved to be a difficult reagent to work with, since it has a large molecular weight, with a maximum solution concentration in THF of around 0.1 mol dm^{-3}. The high dilution required in these reactions combined with the air and moisture sensitive nature of this reagent, results in even minimal scale-up becoming problematic.

2.3.9 An alternative synthesis of key cyclopropane carboxaldehyde

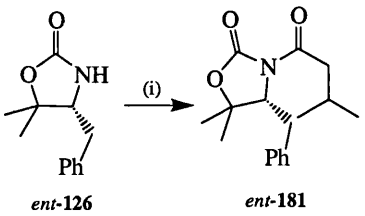
At this stage of the project, observations on a number of aldol substrates under different *retro*-aldol conditions had revealed that even small changes in the steric demand of the aldol substrate had a dramatic effect on the yield and rate of the *retro*-aldol reaction. For example, replacing the α-methyl group of the aldol substrate with a more sterically hindered phenyl group in *syn*-aldol **164a** (**Table 2.3-1**), dramatically increased the rate of the *retro*-aldol reaction, although it is likely that electronic stabilisation of the enolate may also play an important role in this case.



Scheme 2.3-28 – *Unwanted retro-aldol reaction of α-phenyl syn-aldol over silica gel*

Unfortunately, the propensity of this substrate to undergo a facile *retro*-aldol reaction also meant that this *syn*-aldol was unstable to silica gel chromatography. In contrast, saturated *syn*-aldol **134**, which does not contain the increased steric demand of the cyclopropyl group, failed to undergo a *retro*-aldol reaction under our thermal and samarium(II) iodide conditions. It was concluded that the *retro*-aldol reaction might be improved by simply increasing the steric demand of the chiral auxiliary fragment at its α-position.

Therefore, *N*-isopropyl oxazolidin-2-one **181** was prepared as a new chiral auxiliary *via* reaction of the lithium anion of oxazolidin-2-one *ent*-**126** with isovaleryl chloride under our standard conditions in 87% yield (**Scheme 2.3-29**).

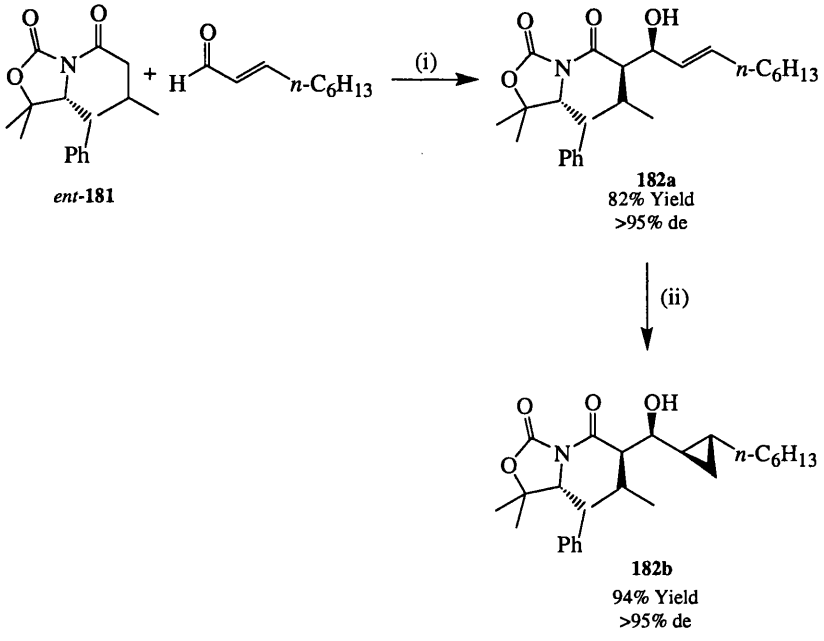


ent-**126** *ent*-**181**

Reagents and conditions: (i) ^{n}BuLi, isovaleryl chloride, THF, -78 to 0°C.

Scheme 2.3-29 – *Synthesis of α-isopropyl oxazolidin-2-one 181*

This boron enolate of α-isopropyl oxazolidin-2-one **181** was then reacted with (*E*)-non-2-enal under our standard *syn*-aldol conditions (9BBN-OTf, $^{i}Pr_2NEt$), to afford α-isopropyl *syn*-aldol **182a** in >95% de and 82% yield. This *syn*-aldol **182a** was then cyclopropanated using Charette's modified Furukawa conditions to afford the α-isopropyl cyclopropyl *syn*-aldol **182b** in >95% de and isolated in 94% yield. Therefore, it was demonstrated that substitution of an α-methyl group for a more sterically demanding α-isopropyl group had failed to alter the stereoselectivity of these two highly diastereoselective reactions.



ent-**181**

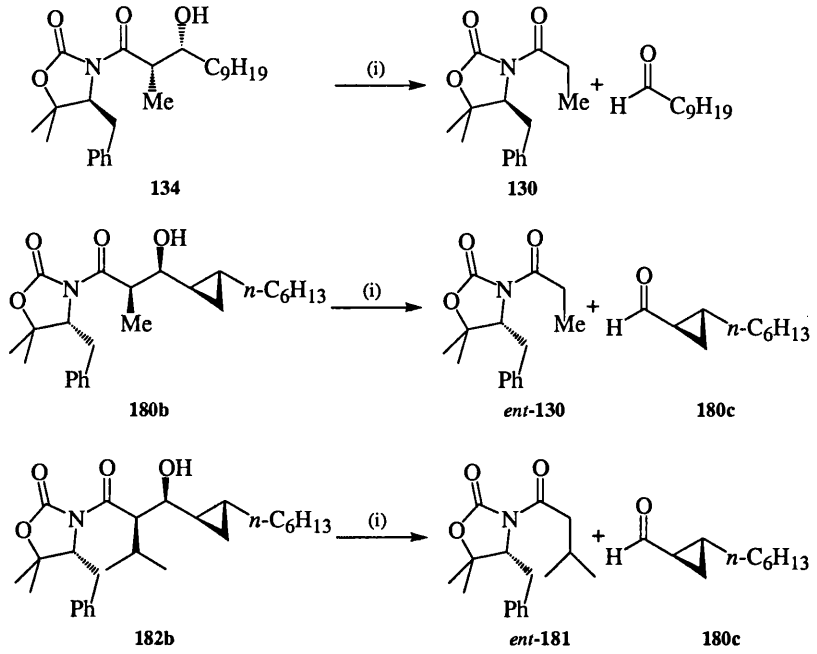
182a
82% Yield
>95% de

182b
94% Yield
>95% de

Reagents and conditions: (i) 9BBN-OTf, $^{i}Pr_2NEt$, CH_2Cl_2, 0°C, then –78 to RT, (E)-non-2-enal; (ii) Et_2Zn, CH_2I_2, CH_2Cl_2, -10 to 0°C, 2 hours.

Scheme 2.3-30 – *Synthesis of α-isopropyl cyclopropyl syn-aldol 182b*

The anionic *retro*-aldol reaction of α-isopropyl cyclopropyl *syn*-aldol **182b** was then compared with the corresponding *retro*-aldol reactions of α-methyl-β-alkyl-*syn*-aldol **134** and α-methyl cyclopropyl *syn*-aldol **180b**, under conditions that had previously been shown to be low yielding in the *retro*-aldol reaction (**Scheme 2.3-31**).

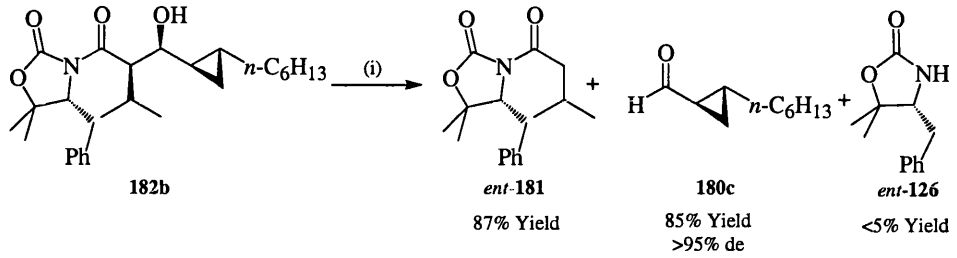


Reagents and conditions: (i) KHMDS, THF.

Scheme 2.3-31 – *Comparison of sterics in the retro-aldol reaction*

Treatment of α-methyl-β-alkyl-*syn*-aldol **134** with KHMDS in THF at -78°C resulted in essentially no *retro*-aldol reaction occurring as determined from examination of the crude 300 MHz ^{1}H-NMR spectrum. α-Methyl cyclopropyl *syn*-aldol **180b** under these conditions was cleaved to give approximately 5% conversion to the desired cyclopropane carboxaldehyde product **180c**; whilst α-isopropyl cyclopropyl *syn*-aldol **182b** was cleaved to afford 17% conversion to the desired *retro*-aldol products. Raising the temperature to -40°C, it was found that α-methyl-β-alkyl-*syn*-aldol **134** still gave less than 5% conversion to its *retro*-aldol products, α-methyl cyclopropyl *syn*-aldol **180b** proceeded in 16% conversion, whilst α-isopropyl cyclopropyl *syn*-aldol **182b** resulted in 72% conversion under these conditions. Finally, increasing the reaction time to three hours, the *retro*-aldol reaction of α-isopropyl cyclopropyl *syn*-

aldol **182b** at -40°C resulted in complete conversion to the desired (1*R*,2*R*)-2-hexylcyclopropanecarbaldehyde **180c** in 85% yield with less than 5% competing formation of oxazolidin-2-one *ent*-**126** being observed (**Scheme 2.3-32**).



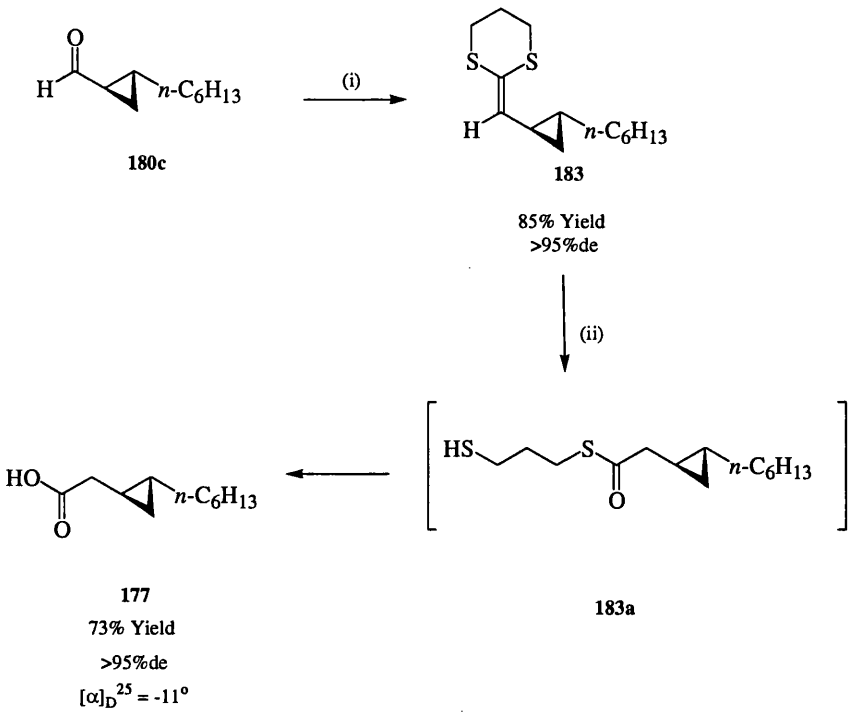
Reagents and conditions:(i) KHMDS, THF, -40°C, 3 hours.

Scheme 2.3-32 – *Efficient retro-aldol cleavage of α-isopropyl cyclopropyl syn-aldol **182b***

2.3.10 An efficient synthesis of *Cascarillic acid*

With the desired cyclopropane carboxaldehyde **180c** in hand, it was necessary to carry out an oxidative one-carbon homologation to afford *Cascarillic acid* **177**. Using methodology first established by Corey *et al*,[131] treatment of (1*R*,2*R*)-2-hexylcyclopropanecarbaldehyde **180c** with the lithium anion of (1,3-dithian-2-yl)trimethylsilane resulted in nucleophilic addition of the dithiane to the aldehyde functionality, followed by subsequent Peterson elimination, to afford 2-(((1*R*,2*R*)-2-hexylcyclopropyl)methylene)-1,3-dithiane **183** in >95% de and 93% yield. This reaction was successful in establishing the correct oxidation state of the homologated carbon atom, and no evidence of any epimerisation of the cyclopropane ring was observed. Treatment of ketene thioacetal **183** under acidic hydrolysis conditions failed to hydrolyse the compound to the desired carboxylic acid **177**, instead affording thioester **183a** in good yield as determined by ^{1}H-NMR spectroscopy. However, sequential treatment of ketene thioacetal **183** under acid and base catalysed hydrolysis conditions[132] gave *Cascarillic acid* **177** in >95% de and 78% yield, whose spectroscopic data matching that previously published for this compound.[126] The negative sign obtained for the specific rotation of my sample of *Cascarillic acid* **177**

($[\alpha]_D^{25}$ = -11), compared well with the reported value ($[\alpha]_D^{lit.}$ = -10.9), thus confirming that the correct enantiomer of the natural product had been prepared.[133]



180c

183

85% Yield
>95%de

183a

177
73% Yield
>95%de
$[\alpha]_D^{25}$ = -11°

*Reagents and conditions: (i) ^{n}BuLi, (1,3-dithian-2-yl)trimethylsilane, THF, 0°C, 1 hour, then (1R,2R)-2-hexylcyclopropanecarbaldehyde **180c**, -30°C, 2 hours; (ii) p-TSA, THF/H_2O, 6 hours, then KOH, Acetone/H_2O, 2 hours.*

Scheme 2.3-33 – *One carbon homologation of cyclopropane carboxaldehyde **180c** to afford Cascarillic acid **177***

2.3.11 Conclusion

Optimisation studies on the *retro*-aldol reaction of *N*-acyl-oxazolidin-2-one *syn*-aldols resulted in anionic, thermal and samarium(II) iodide mediated conditions being developed that afford chiral cyclopropane carboxaldehyde products in acceptable yields. These optimisation studies enabled an efficient asymmetric synthesis of the cyclopropane natural product *Cascarillic acid* **177** to be carried out in only five steps as a single enantiomer in 41% overall yield.

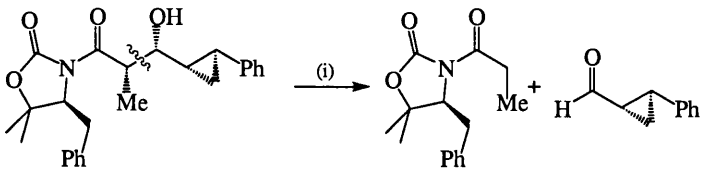
Chapter 2.4 An alternative elimination strategy for using temporary stereocentres in asymmetric synthesis

2.4.1 Introduction

In this chapter, an alternative strategy for using *temporary stereocentres* to relay stereochemical information will be described. In this regard, conditions for the diastereoselective synthesis of α-chloro-β-hydroxy cyclopropyl *syn*-aldols have been established, and their subsequent samarium(II) iodide mediated elimination reaction described. This new methodology has been applied to the total synthesis of another cyclopropane containing natural product, *Grenadamide*. Further attempts towards exploiting this new methodology for the asymmetric synthesis of structurally challenging oligomeric cyclopropane motifs will then be described, based on an iterative aldol/directed cyclopropanation/samarium(II) elimination strategy for stereocontrol.

2.4.2 A new *temporary stereocentre* strategy for asymmetric synthesis

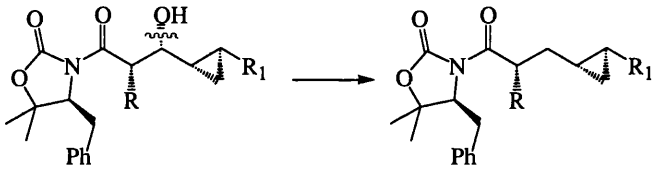
The previous strategy employed for the three-step synthesis of *chiral aldehydes*, involved a final cleavage step of the aldol bond *via* a *retro*-aldol reaction, which destroyed the directing *temporary stereocentre* to afford chiral cyclopropane carboxaldehydes (**Scheme 2.4-1**).



Reagents and conditions: (i) LiHMDS, toluene, 5°C, 2 hours.

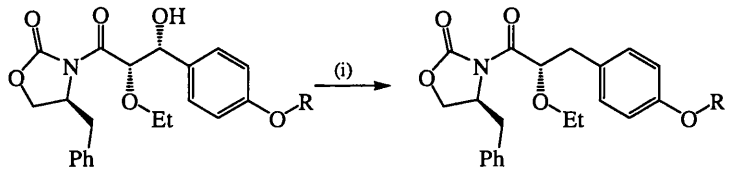
Scheme 2.4-1 – *Retro-aldol cleavage to remove the temporary stereocentre*

To expand our methodology for using *temporary stereocentres* to generate remote chirality, we chose to investigate alternative cleavage strategies for their removal. It was proposed that this could be achieved by cleaving the carbon-oxygen bond of the aldol substrate, thus affording access to a new class of chiral cyclopropane products (**Scheme 2.4-2**).



Scheme 2.4-2 – *Proposed new strategy for the removal of temporary centres for synthesis of remote chirality*

A review of the literature revealed that Haigh and co-workers had demonstrated that reduction of the β-hydroxyl functionality of *N*-acyl-oxazolidin-2-one *syn*-aldol **184** could be carried out using silyl hydride methodology (**Scheme 2.4-3**).[134]

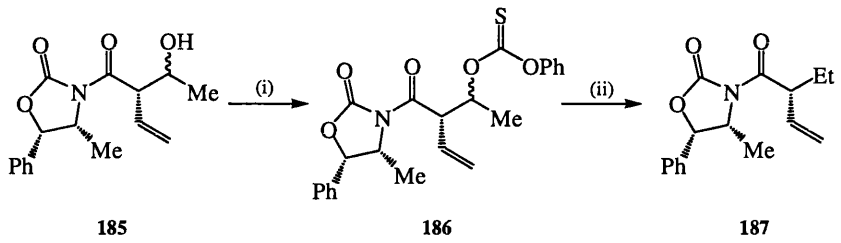


184

Reagents and conditions: (i) Et_3SiH, CF_3CO_2H, 4 days.

Scheme 2.4-3 – *Silyl hydride reduction of β-hydroxy syn-aldols*

Alternatively, Wee and co-workers had carried out a radical reduction on *syn*-aldol **185**, *via* formation of its phenyl thiocarbonate **186** and reduction with Bu_3SnH, to afford chiral *N*-acyl-oxazolidin-2-one **187** in 75% yield, with no evidence of any competing rearrangement products (**Scheme 2.4-4**).[135]



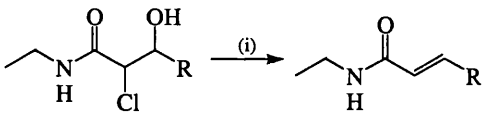
185 **186** **187**

Reagents and conditions: (i) PhOC(=S)Cl, DMAP, CH_2Cl_2; (ii) Bu_3SnH, AIBN, toluene.

Scheme 2.4-4 – *Radical -cleavage of thiocarbamates*

These two transformations required either formation of a reactive carbocation like intermediate at the β-position of aldol **184** (**Scheme 2.4-3**) or a radical intermediate at the β-position of aldol **185** (**Scheme 2.4-4**). Application of these methodologies to our new strategy for the synthesis of chiral cyclopropanes was unlikely to be successful since both would result in formation of reactive intermediates allylic to the cyclopropane ring, which would result in unwanted cleavage of the cyclopropane ring.[136,137]

Therefore, removal of the hydroxyl group of a *syn*-aldol product that was allylic to a cyclopropane ring appeared to be a non-trivial transformation, since the methodology to replace hydroxyl groups with hydrogen atoms in this manner generally required either the use of strong acids to generate carbocations, or relied upon free radical chemistry. However, a review of the literature for alternative strategies to effect this transformation revealed recent work by Concellon and co-workers who had described a highly diastereoselective samarium(II) iodide mediated elimination of α-chloro-β-hydroxyamides (**Table 2.4-1**).[138]

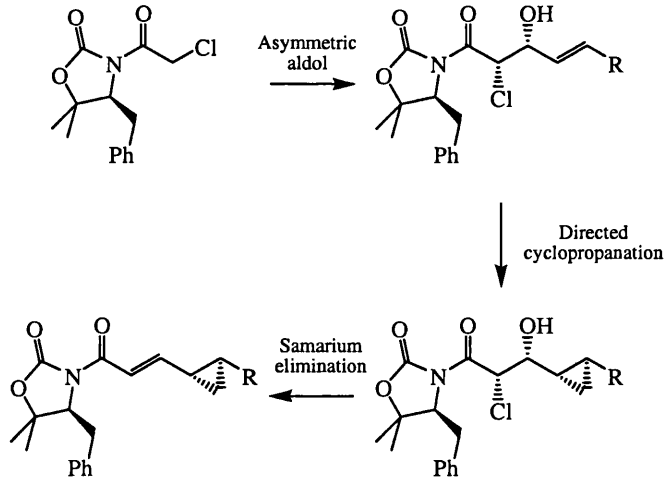


Entry	*Amide*	*R*	*de (%)*	*Yield*
1	**188**	Ph	>98	90
2	**189**	C_7H_{15}	>98	89
3	**190**	MeCH(Ph)	>98	82

Reagents and conditions: (i) SmI_2, THF, RT, 30 minutes.

Table 2.4-1 – *Samarium(II) iodide elimination of α-chloro-β-hydroxyamides*

This β-elimination reaction was shown to proceed with excellent (*E*)-diastereoselectivity and in high yields, which had been applied to a variety of α-chloro-β-hydroxyamides.[139] Furthermore, it was proposed that this methodology was less likely to result in formation of an intermediate containing a reactive species allylic to the cyclopropane ring during cleavage of the hydroxyl functionality. Therefore, a *retro*-synthetic strategy was proposed that relied on a key samarium(II) iodide mediated elimination reaction of an α-chloro cyclopropyl *syn*-aldol, which would result in the simultaneously removal of two stereocentres. (**Scheme 2.4-5**).[140]



Scheme 2.4-5 – *Proposed elimination strategy for the synthesis of chiral cyclopropanes*

A review of the literature revealed that this approach appeared ideally suited to the asymmetric synthesis of another cyclopropane containing natural product,

Grenadamide, the structure and previous synthesis of which is described in the following section.

2.4.3 The previous total synthesis of *Grenadamide*

Grenadamide **191**, *Debromogrenadadiene* **192** and *Grenadadiene* **193** **(Figure 2.4-1)** are natural products isolated from the marine cyanobacterium *Lyngbya majuscula* by Sitachitta and Gerwick in 1998.[141] These structurally unique cyclopropyl fatty acid metabolites demonstrated cannabinoid receptor activity and cytotoxicity towards cancer cells.

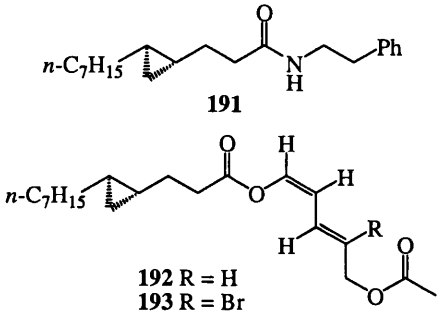
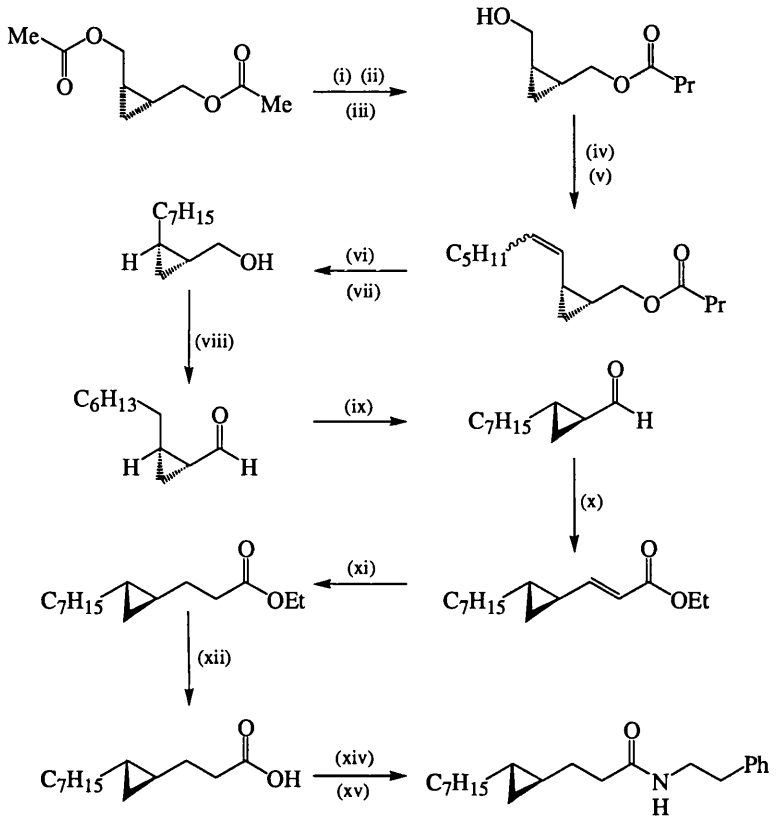


Figure 2.4-1 – *Grenadamide, Debromogrenadadiene and Grenadadiene*

Baird and co-workers subsequently confirmed the absolute stereochemistry of the cyclopropane fragment of *Grenadamide* **191** as (*R,R*) *via* total synthesis of the wrong enantiomer of this natural product.[142] Their approach required fifteen linear steps, using an enzymatic desymmetrisation reaction to introduce chirality,[143] and an epimerisation reaction to establish the *trans*-configuration of the cyclopropane ring **(Scheme 2.4-6)**.



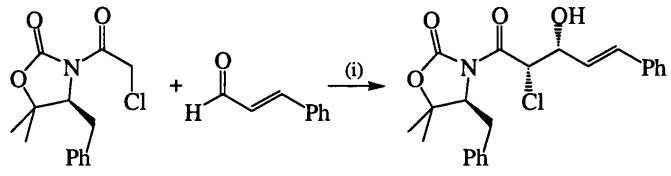
Reagents and conditions: (i) $LiAlH_4$, THF; (ii) PrOCl, DMAP, THF; (iii) PPL, H_2O/ethylene glycol, pH 6.5; (iv) PCC, CH_2Cl_2; (v) $Br^-P^+Ph_3(CH_2)_5Me$, BuLi, THF -78°C; (vi) K_2CO_3, MeOH (vii) N_2H_4, ^iPrOH, $NaIO_4$, CH_3COOH, $CuSO_4$, (viii) PCC, CH_2Cl_2; (ix) NaOMe, MeOH; (x) $Ph_3PCHCOOEt$, toluene; (xi) $KO_2CN{=}NCO_2K$, AcOH, MeOH; (xii) KOH, EtOH, water; (xiii) $SOCl_2$; (xiv) $PhCH_2CH_2NH_2$.

Scheme 2.4-6 – *Baird's synthesis of the wrong enantiomer of Grenadamide*

We considered that this approach was once again an overly complicated synthesis for such a simple natural product that contained only two stereocentres. We therefore decided to apply the new *temporary stereocentre* strategy previously outlined in this chapter to the asymmetric total synthesis of *Grenadamide* **191**.

2.4.4 Model studies on the asymmetric *syn*-aldol and cyclopropanation reactions of α-chloro oxazolidin-2-one auxiliaries

As had been previously observed in our studies on the three-step synthesis of cyclopropane carboxaldehydes, the nature of the α-substituent of the *N*-acyl-oxazolidin-2-one had the potential to adversely affect the diastereoselectivity of the subsequent *syn*-aldol reaction. In this respect, the effect of having an α-chloro substituent on the subsequent cyclopropanation reaction was also unknown. We therefore undertook a model study to establish reagents and conditions for both these protocols. α-Chloro oxazolidin-2-one auxiliary **166** was synthesised by the previously described method using chloroacetyl chloride as an acylating reagent in 81% yield. This compound was then reacted under our standard aldol conditions (9BBN-OTf, $^{i}Pr_2NEt$) with (*E*)-cinnamaldehyde, to afford the α-chloro-β-vinyl-*syn*-aldol **194a** in only 80% de as determined by examination of the crude 300 MHz ^{1}H-NMR spectrum. Disappointed by this result, the Lewis' acid source was changed to dibutyl boron triflate, which under the same conditions gave the desired α-chloro β-vinyl *syn*-aldol **194a** in 92% de, which was purified to >95% de by recrystallisation in 83% yield (**Scheme 2.4-7**).



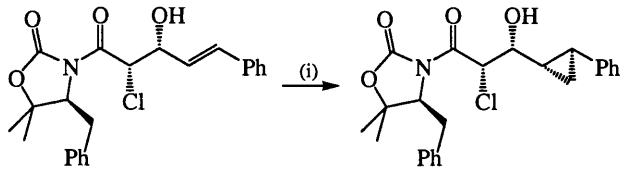
166 **194a**

Reagents and conditions: Dibutyl boron triflate, $^{i}Pr_2NEt$, CH_2Cl_2, 0°C, 1 hour, (E)-cinnamaldehyde, -78 to RT, overnight.

Scheme 2.4-7 – *Asymmetric syn-aldol reaction of α-chloro oxazolidin-2-one auxiliary*

The α-chloro-β-vinyl-*syn*-aldol **194a** was then cyclopropanated under our standard conditions to give the desired α-chloro cyclopropyl *syn*-aldol **194b** in >95% de and

94% yield. Therefore, it had been demonstrated that the α-chloro substituent was stable to our cyclopropanation conditions, and had exhibited no detrimental effect on the diastereoselectivity of the reaction (**Scheme 2.4-8**).



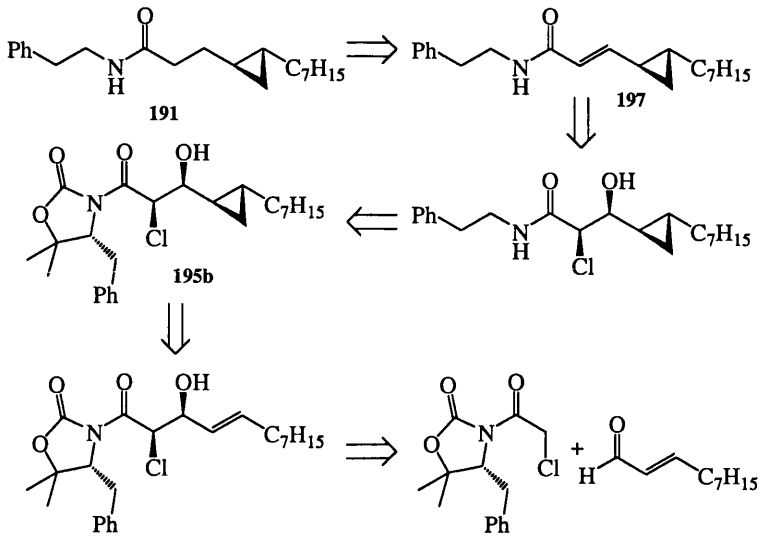
194a **194b**

Reagents and conditions: (i) Et_2Zn, CH_2I_2, CH_2Cl_2, -20 to 0°C, 2 hours.

Scheme 2.4-8 – *Cyclopropanation of α-chloro-β-vinyl syn-aldol*

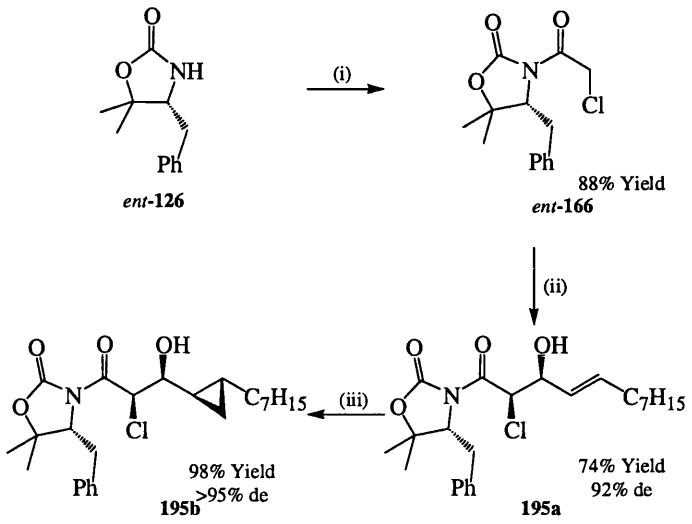
2.4.5 An efficient asymmetric total synthesis of *Grenadamide*

We therefore sought to apply this new methodology to the total synthesis of *Grenadamide* **191** using the *retro-syn*thetic analysis described in **Scheme 2.4-9**. A key reaction in this *retro*-synthetic analysis would involve the direct aminolysis of the oxazolidin-2-one fragment of α-chloro *syn*-aldol **195b** with phenylethylamine,[144] in which the oxazolidin-2-one carbonyl would be protected from endocyclic cleavage by the presence of their 5,5-dimethyl substituents of the oxazolidin-2-one ring. A second important reaction would be the samarium(II) iodide mediated elimination of the α-chloro and β-hydroxyl substituents, as well the development of conditions to hydrogenate the alkene functionality of **197**, in the presence of a cyclopropane ring.[145]



Scheme 2.4-9 – *Retro-synthetic analysis of Grenadamide*

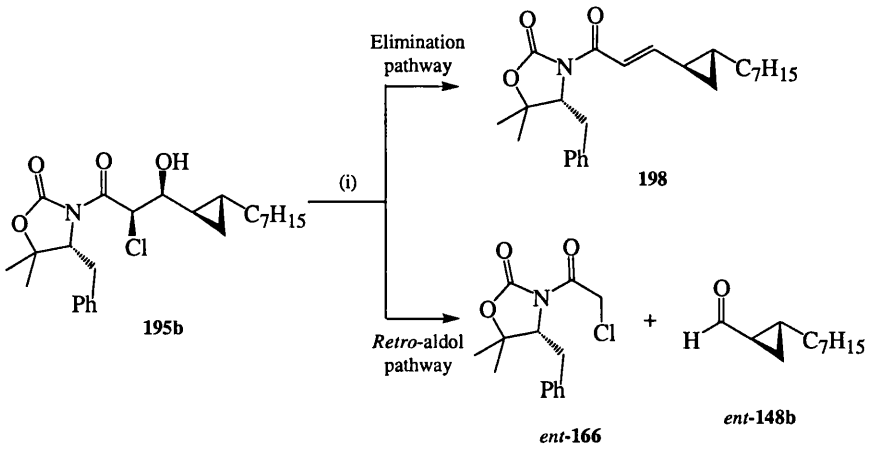
The unnatural (*R*)-enantiomer of oxazolidin-2-one auxiliary *ent*-**126** was *N*-acylated with chloroacetyl chloride under our standard conditions to give α-chloro oxazolidin-2-one *ent*-**166** in 88% yield. This chiral auxiliary was then subjected to our modified *syn*-aldol conditions (Bu_2BOTf, $^iPr_2NEt$) with (*E*)-dec-2-enal to afford the desired α-chloro-β-vinyl-*syn*-aldol **195a** in 92% de, which was purified to >95% de in 74% yield following silica gel chromatography. The α-chloro-β-vinyl *syn*-aldol **195a** was then cyclopropanated under our standard conditions to afford the desired α-chloro cyclopropyl *syn*-aldol **195b** in >95% de and 98% yield (**Scheme 2.4-10**).



Reagents and conditions: (i) ^{n}BuLi, chloroacetyl chloride THF, -78 to 0°C, 2 hours; (ii) dibutyl boron triflate, $^{i}Pr_2NEt$, CH_2Cl_2, 0°C, 1 hour, (E)-dec-2-enal, -78 to RT, overnight; (iii) Et_2Zn, CH_2I_2, CH_2Cl_2, -10 to 0°C, 2 hours.

Scheme 2.4-10 – *Synthesis of α-chloro cyclopropyl syn-aldol **195b***

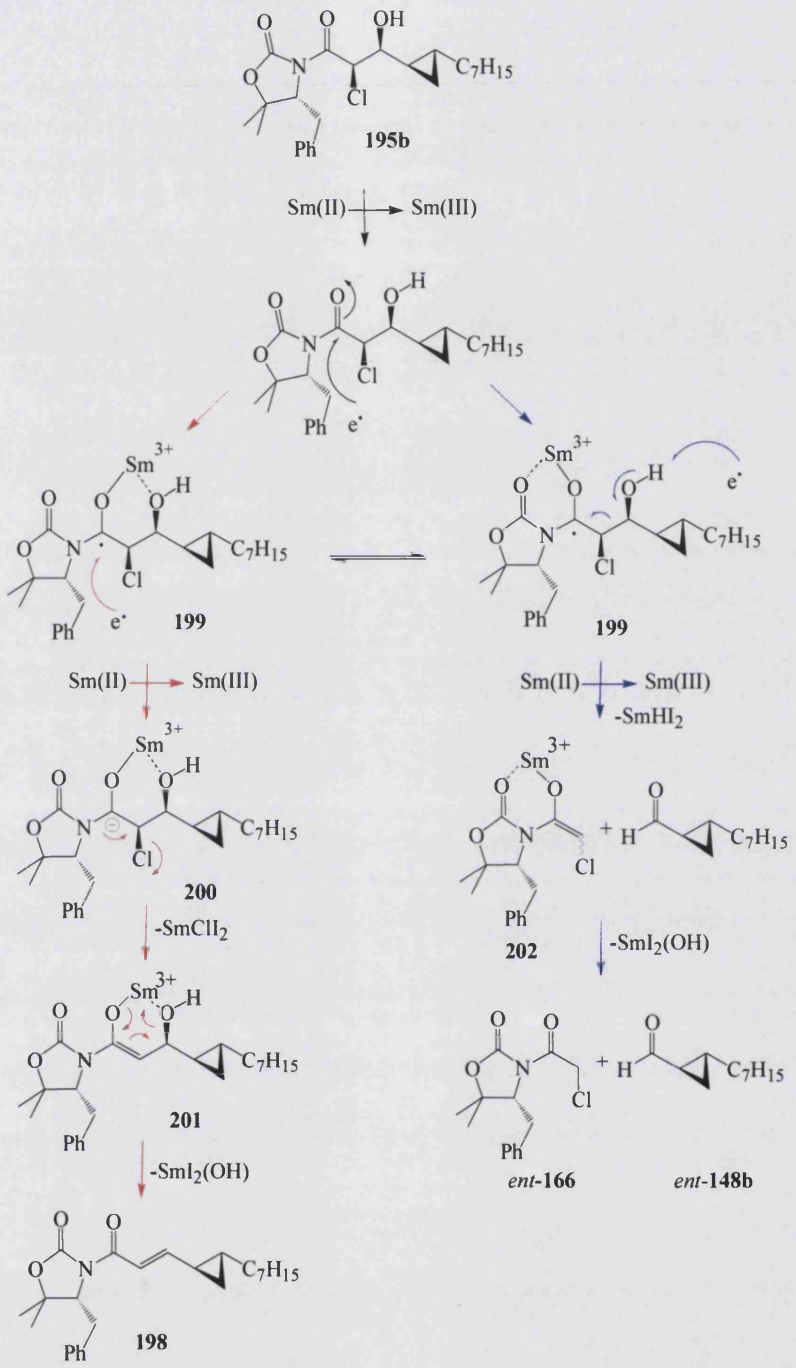
It was then necessary to simultaneously eliminate the α-chloro and β-hydroxy substituents of cyclopropyl *syn*-aldol **195b** to ideally afford an (*E*)-alkene fragment in high de. Treatment of α-chloro cyclopropyl *syn*-aldol **195b** with three equivalents of samarium(II) iodide gave the desired α,β-unsaturated cyclopropane **198** in only 60% yield, as determined from examination of the crude 300 MHz ^{1}H-NMR spectrum, with the remaining mass balance being comprised of products from a *retro*-aldol reaction (**Scheme 2.4-11**).



Reagents and conditions: (i) SmI_2 (3 eq.) THF, RT, 1 hour.

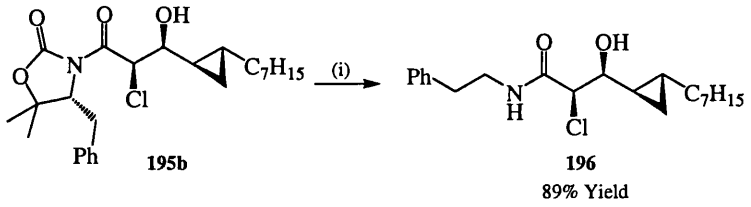
Scheme 2.4-11 – *Samarium mediated elimination of α-chloro syn-aldol*

Two competing reaction pathways were therefore proposed to be occurring through a common intermediate arising from radical reduction of the exocyclic carbonyl of α-chloro cyclopropyl *syn*-aldol **195b** (**Scheme 2.4-12**). Samarium(II) is oxidised to samarium(III) with the release of an electron that reacts with *syn*-aldol **195b** to afford a common radical anion intermediate **199**,[146] This radical enolate intermediate **199** can then be reduced father, to afford anionic intermediate **200** (red arrow), which then proceeds *via* the expected elimination pathway. Firstly, the α-chloro substituent is eliminated from intermediate **200**, to afford samarium(III) enolate **201**, which then undergoes samarium(III) mediated $E1_cb$ type elimination of the β-hydroxyl group, to afford the desired α,β-unsaturated oxazolidin-2-one **198**.[147] Alternatively, the second equivalent of samarium(II) can abstract a proton from common radical intermediate **199** (blue arrow),[125] which then initiates a radical *retro*-aldol reaction to afford *ent*-cyclopropane carboxaldehyde *ent*-**150c** and samarium(III) enolate **203**, which would tautomerise during work-up, to afford α-chloro oxazolidin-2-one auxiliary *ent*-**166**. It was proposed that the formation of radical intermediate **200** is the driving force for this *retro*-aldol reaction, since this type proton abstraction mechanism is unlikely to occur in the absence of this radical enolate.



Scheme 2.4-12 – *Proposed mechanism for the radical elimination and retro-aldol reactions of cyclopropyl aldol* ***195b***

As described earlier in this thesis, *retro*-aldol reactions under samarium(II) iodide mediated conditions have not been reported previously; however, it was noted that all Concellon's previous reports on elimination reactions had been carried out on simple α-chloro β-hydroxy amides, esters and ketone substrates. It was proposed therefore that the presence of the oxazolidin-2-one fragment of these types of *syn*-aldol substrates must have been acting to promote this unique *retro*-aldol reaction pathway. We therefore chose to remove the oxazolidin-2-one auxiliary fragment of *syn*-aldol **195b** to afford secondary amide intermediate **196**, which it was then hoped would undergo a clean β-elimination reaction. Davies and co-workers had previously shown that *N*-acyl derived 3,3-dimethyl-pyrrolidin-2-one chiral auxiliaries underwent clean aminolysis reactions with primary amines.[144] Therefore, α-chloro cyclopropyl *syn*-aldol **195b** was dissolved in neat phenylethylamine and stirred overnight, which resulted in cleavage of the oxazolidin-2-one auxiliary ***ent*-126** to afford the desired α-chloro cyclopropyl amide **196** as the only product in 89% yield after silica gel chromatography (**Scheme 2.4-13**).



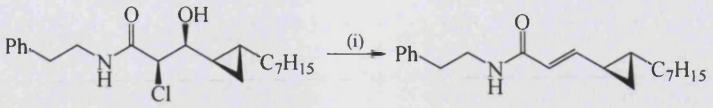
195b **196**

89% Yield

Reagents and conditions: (i) phenylethylamine (neat), overnight.

Scheme 2.4-13 – *Aminolysis of α-chloro cyclopropyl aldol **195b***

Importantly, no competing side products arising from nucleophilic displacement of the α-chloro group by the amine or competing nucleophilic attack at the endocyclic carbonyl were observed in this reaction. This new α-chloro β-hydroxy cyclopropyl amide **196** was then treated with samarium(II) iodide in THF to afford the desired α,β-unsaturated cyclopropyl amide **197** in 85% yield and >95% de, with no competing products arising from the *retro*-aldol reaction being observed in this case (**Scheme 2.4-14**).



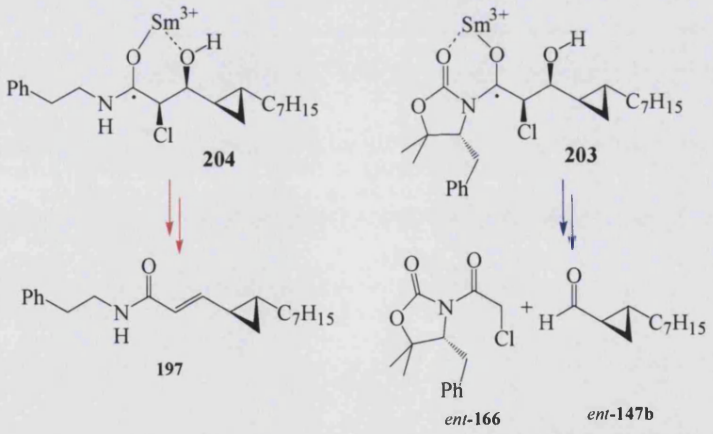
196 **197**

85% Yield
>95% de

Reagents and conditions: SmI_2 (3 eq.), THF, RT, 30 minutes.

Scheme 2.4-14 – *Samarium(II) iodide mediated elimination of cyclopropyl amide **196***

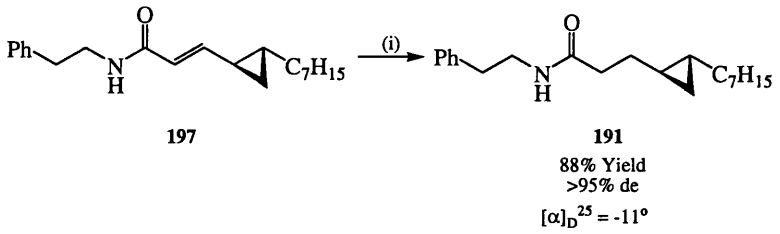
In order to explain the change in reactivity between *N*-acyl-oxazolidin-2-one derived *syn*-aldol **195b** and secondary amide **196**, it was proposed that coordination of the samarium(III) species to the β-hydroxyl functionality is essential for an efficient β-elimination reaction to occur. Competing coordination of samarium(III) to the oxazolidin-2-one carbonyl of intermediate **203**, decreases the rate of this elimination reaction, and as a consequence, the rate of the competing *retro*-aldol reaction pathway becomes significant. In samarium(III) amide complex **204**, this type of interaction cannot occur, so only products arising from the β-elimination pathway are observed (**Scheme 2.4-15**).



Reagents and conditions: SmI_2 (3 eq.), THF, RT, 1 hour.

Scheme 2.4-15 – *Proposed change in reaction pathway in samarium(II) mediated elimination and retro-aldol reactions*

The alkene fragment of α,β-unsaturated amide **197** was then reduced *via* treatment with sodium borohydride and cobalt(II) chloride in methanol/THF,[148] to afford (*R,R*)-*Grenadamide* **191** in 88% yield and >95% de.[149] The spectroscopic data of this sample of (*R,R*)-*Grenadamide* **191** matched that previously published for this natural product; whilst the specific rotation of $[\alpha]_D^{25} = -11$ ($[\alpha]_D^{lit.} = -11$) [150] confirmed we had synthesised the correct enantiomer of this natural product. We had therefore completed the asymmetric synthesis of *Grenadamide* in six steps and 42% overall yield from oxazolidin-2-one *ent*-**126** (**Scheme 2.4-16**).[151]



197

191
88% Yield
>95% de
$[\alpha]_D^{25} = -11°$

Reagents and conditions: (i) $NaBH_4$ (4eq.), $CoCl_2$ (20 mol%), DMF, RT, 2 hours.

Scheme 2.4-16 – *Conjugate reduction of α,β-unsaturated amide to Grenadamide* ***191***

2.4.6 Temporary stereocentre methodology for the asymmetric synthesis of oligomeric cyclopropanes

In the previous section the application of our new temporary stereocentre strategy to the asymmetric synthesis of the cyclopropane containing natural product Grenadamide was discussed. We wished to expand this methodology to more complicated natural product targets by exploiting the excellent diastereoselectivity of the samarium(II) iodide elimination reaction for the synthesis of oligocyclopropane motifs.

2.4.7 Oligomeric cyclopropanes

The natural products *FR-900848* **205** and *U-106305* **206** (**Figure 2.4-2**) were first isolated by Yoshida and co-workers in 1990 from the fermentation broth of *Streptoverticilium fervens* and have demonstrated reasonable antifungal activity against filamentous fungi.[152] However, full structural elucidation was not achieved until Barrett and co-workers confirmed the configuration of their cyclopropane rings *via* total synthesis in 1997.[153]

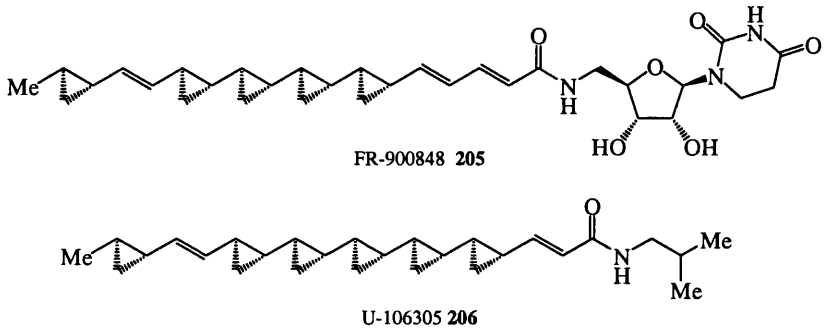
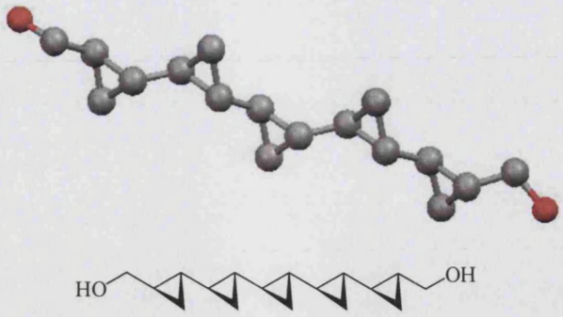


Figure 2.4-2 – *Oligocyclopropyl containing natural products*

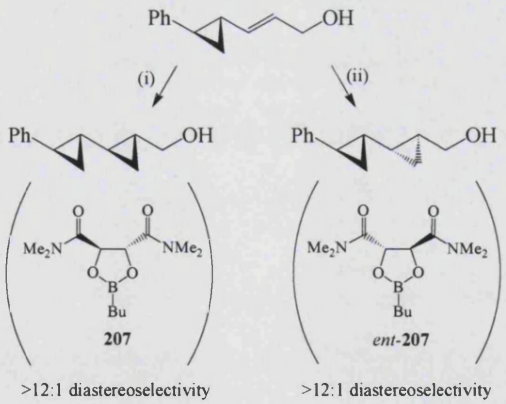
Additionally, this oligocyclopropane structural motif is also of structural interest, since it displays helical chirality due to the cyclopropane ring of each vicinal *trans-syn*-cyclopropanes adopting a conformation that minimises eclipsing interactions with the adjacent cyclopropane ring. This type of secondary structure represents a rare example of helical architecture that does not rely on hydrogen bonding and as a consequence, these types of oligomeric cyclopropanes have potential applications as chiral ligands or chiral membrane mimics (**Figure 2.4-3**).[154]



Hydrogens omitted for clarity; Grey = Carbon, Red = Oxygen.

Figure 2.4-3 – *X-ray crystal structure displaying helical chirality of trans-syn-quincyclopropane*

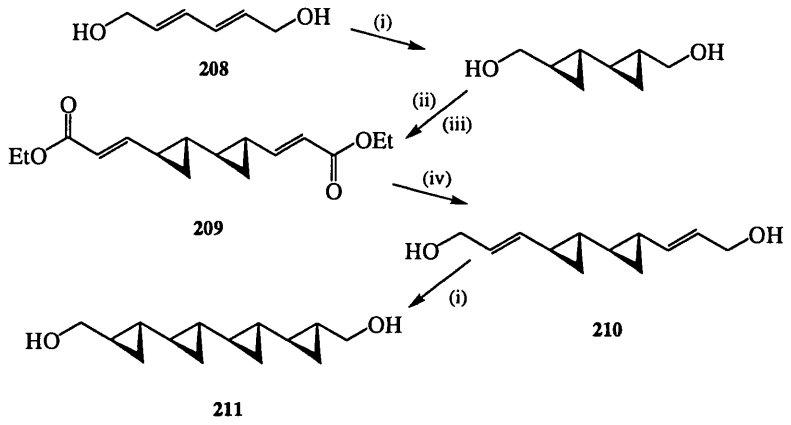
Barrett demonstrated that the key to the synthesis of these types of natural products was stereoselective formation of the challenging core oligocyclopropyl functionality, which was carried out using an iterative strategy.[155] Each successive enantioselective cyclopropanation reaction was achieved using methodology developed by Charette and co-workers,[156] employing chiral boron tartramide additives **207** and *ent*-**207** to form a diastereomeric complex for the enantioselective cyclopropanation of allylic alcohols (**Scheme 2.4-17**).[157]



*Reagents and conditions: (i) Et_2Zn, CH_2I_2, **207**, CH_2Cl_2; (ii) Et_2Zn, CH_2I_2, **ent-207**, CH_2Cl_2.*

Scheme 2.4-17 – *Boron-tartramide mediated enantioselective cyclopropanation of allylic alcohols*

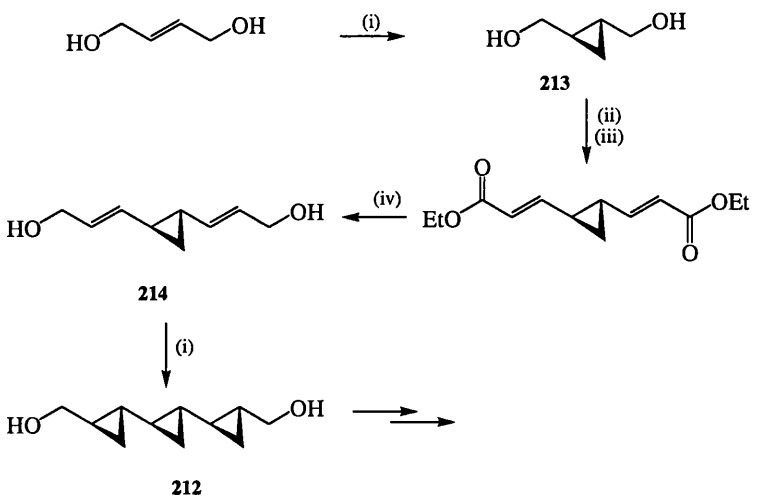
Barrett and co-worker used this chiral boron tartramide methodology to carry out enantioselective cyclopropanation reactions of the two allylic alcohol functionalities of mucandiol **208** in high yield and stereoselectivity. Subsequent oxidation and homologation of the resulting aldehyde functionality using Wadsworth-Emmons olefination chemistry afforded vinyl-cyclopropane **209**. This was then reduced to diol **210** before a second iteration of the enantioselective chiral boron tartramide cyclopropanation reaction, to afford quartcyclopropane diol **211** (**Scheme 2.4-18**).



Reagents and conditions: (i) (4S,5S)-207, Et_2Zn, CH_2I_2, CH_2Cl_2, 0 to 25°C; (ii) PCC, NaOAc, silica, CH_2Cl_2 0 to 25°C; (iii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, (iv) DIBAL-H, CH_2Cl_2, -78°C.

Scheme 2.4-18 – *Barrett's synthesis of quartcyclopropane*

An alternative strategy for the synthesis of a key triscyclopropane diol **212** is described in **Scheme 2.4-19**. *trans*-Butene-1,4-diol was cyclopropanated using Charette's chiral boron tartramide methodology to afford chiral cyclopropyl diol **213** in 83% yield and 89% ee, which was again homologated using Wadsworth-Emmons chemistry on the corresponding dialdehyde derivative of **213** to afford *bis*-vinyl cyclopropane diol **214**. This compound then underwent subsequent enantioselective cyclopropanation, to afford triscyclopropane diol **212**, which was then elaborated to the natural product *via* a series of iterative protocols.



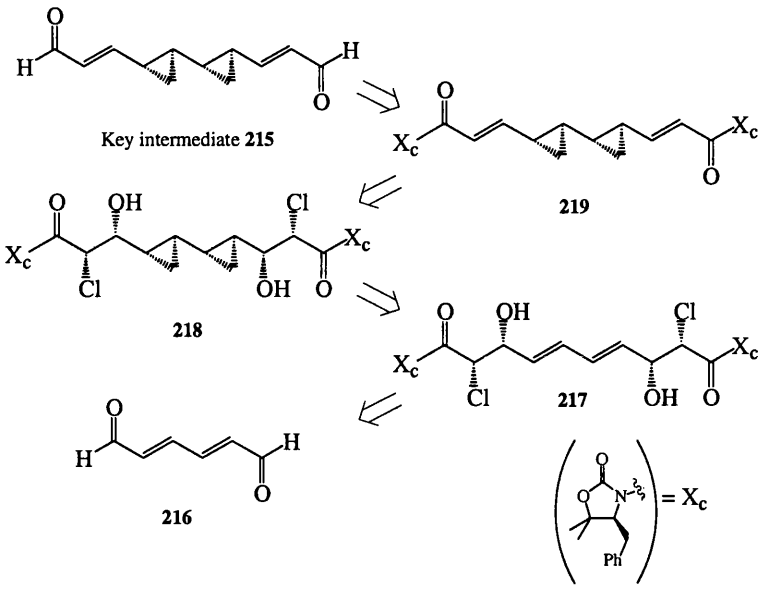
Reagents and conditions: (i) (4S,5S)-207, 4Å molecular sieves, Zn(CH₂I).DME, CH₂Cl₂, -40 to 25°C, Dess-Martin periodinane, pyridine, CH₂Cl₂, then PPh₃; (iii) Ph₃P=CHCO₂Et, CH₂Cl₂, (iv) DIBAL-H, CH₂Cl₂, -78°C.

Scheme 2.4-19 – *Barrett's synthesis of triscyclopropane diol* ***212***

Although this approach proved successful for the synthesis of these structurally challenging natural products, they rely upon the Wadsworth-Emmons olefination reaction for each homologation step, whose (*E*)-/(*Z*)-selectivities were no greater than 8:1 in a number of cases. Therefore, as an alternative we wished to apply our highly stereoselective cyclopropanation/samarium(II) β-elimination methodology described earlier in the chapter for the synthesis of these types of oligomeric cyclopropanes.

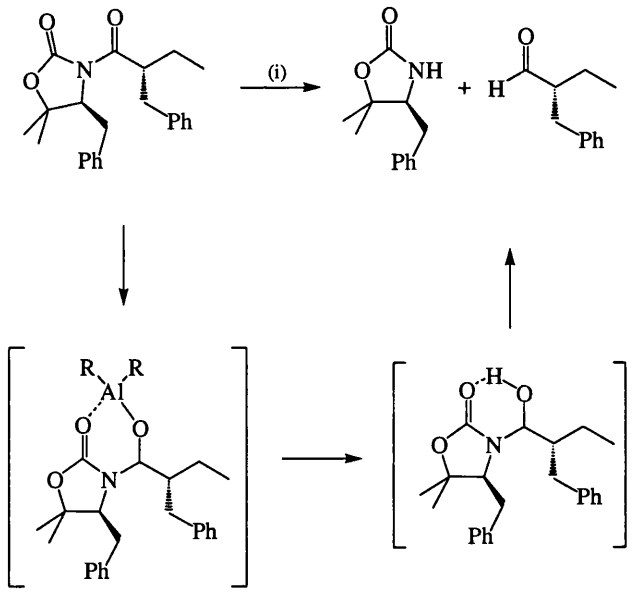
2.4.8 A new synthesis of oligomeric cyclopropanes

An alternative *retro*-synthetic strategy employing a combination of asymmetric aldol/directed cyclopropanation/β-elimination methodology for asymmetric synthesis of key intermediate *bis*-vinyl-cyclopropane **215** was proposed as described in **Scheme 2.4-20**.



Scheme 2.4-20 – *Retro-synthetic analysis of biscyclopropanes*

The key intermediate targeted was *bis*-vinyl-cyclopropane **215**, which would then undergo further iterations to extend the chain length of the oligomeric cyclopropane. This would be achieved by removing the chiral auxiliary (X_c) fragment, *via* treatment with DIBAL-H using the reductive protocol first established by Davies and co-workers,[158] to afford dialdehyde **215**. The 5,5-dimethyl motif of the oxazolidin-2-one ring of **218** had been shown to protect the endocyclic carbonyl from hydride attack in this transformation, ensuring no endocyclic cleavage products were formed. The SuperQuat oxazolidin-2-one fragment acted as an aldehyde equivalent in this reaction, due to the stability of the tetrahedral intermediate **220** arising from chelation of the aluminium counter-ion to the oxazolidin-2-one carbonyl, thus preventing any over-reduction to the corresponding alcohol (**Scheme 2.4-21**).



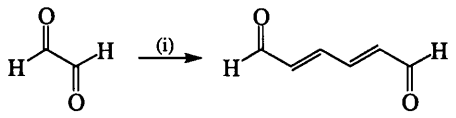
220

Reagents and condition; (i) DIBAL-H, CH_2Cl_2, -78°C, then NH_4Cl.

Scheme 2.4-21 – *Reduction of N-acylated SuperQuat auxiliaries to chiral aldehydes*

It was proposed that the α,β-unsaturated olefin functionality of **218** could be generated *via* treatment of **218** with samarium(II) iodide in high de; whilst disconnection of **217** using a combination of our previously described directed cyclopropanation and *syn*-aldol reactions, reveals mucanaldehyde **216** as the key starting material.

Therefore, mucanaldehyde **216** was synthesised *via* a previously published procedure *via* reaction of glyoxal with the commercially available stabilised Wittig reagent, diphenyl phosphanylidene acetaldehyde (**Scheme 2.4-22**).[159] Attempts to synthesis this compound *via* an oxepin strategy previously described by Davies and co-workers was unsuccessful.[160]



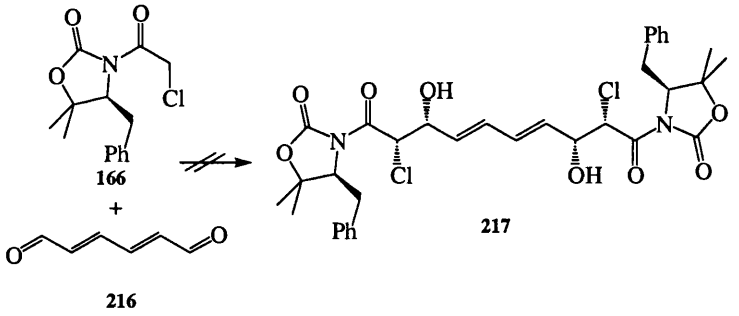
216

62% Yield
>95% de

Reagents and conditions: $CHOCH{=}PPh_3$ (1.95 eq.), DMF, 70°C, 4 hours.

Scheme 2.4-22 – *Synthesis of mucanaldehyde*

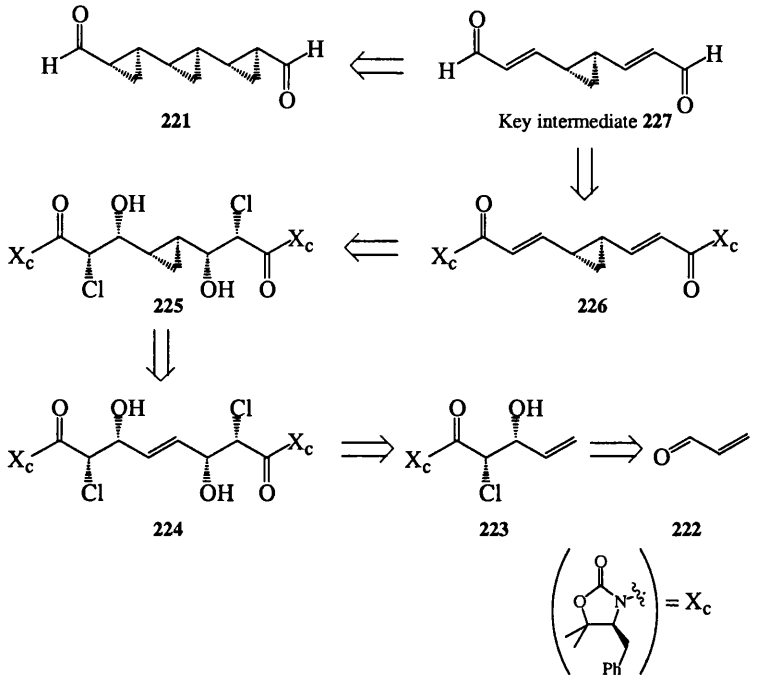
The desired mucanaldehyde **216** was isolated in >95% de and 62% yield following silica gel chromatography, but was found to slowly decompose on standing. Stabilised Wittig reagents are known to be (*E*)-selective, with the high diastereoselectivity of this reaction also being due to equilibration of any (*Z*)-diastereomeric olefin to its thermodynamically more stable (*E*)-isomer under the reaction conditions. We then attempted to react this dialdehyde in a *syn*-aldol reaction with the boron enolate of α-chloro oxazolidin-2-one auxiliary **166** (**Scheme 2.4-23**).



Scheme 2.4-23 – *Attempted syn-aldol reaction of mucanaldehyde*

Reaction of dialdehyde **216** under our standard *syn*-aldol conditions (9BBN-OTf, ^{i}PrNEt; **Scheme 2.2-2**), afforded none of the desired *bis*-aldol **217**, resulting in α-chloro oxazolidin-2-one **166** as the only product recovered. No unreacted dialdehyde **216** was observed on examination of the crude 300 MHz ^{1}H-NMR spectrum, and no other by-products could be isolated from possible further reactions or from decomposition of this compound. We therefore screened a number of alternative conditions for *syn*-aldol reaction, including changing the base to triethylamine, using

dibutyl boron triflate or titanium tetrachloride as Lewis acid sources, as well as lithium enolate formation using LDA as a base; however, in each case only unreacted α-chloro oxazolidin-2-one auxiliary **166** was recovered, with no evidence of any aldol product having been formed. It is likely that the high reactivity of mucanaldehyde **216** meant that it was incompatible with the strong Lewis acid conditions used in these reactions,[161] and as a consequence our attention turned to an alternative strategy for the synthesis of triscyclopropane **221** (**Scheme 2.4-24**).

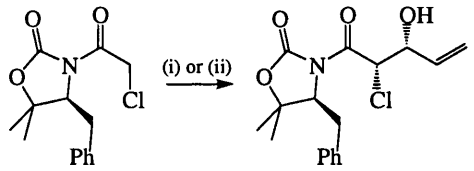


Scheme 2.4-24 – *Retro-synthetic analysis of trimeric cyclopropane*

The key difference in our proposed synthesis of triscyclopropane dialdehyde **221**, would be the synthesis of the double aldol motif of intermediate **224**, which would be achieved from coupling two molecules of α-chloro *syn*-aldol **223** using an intermolecular Grubb's metathesis reaction. α-Chloro *syn*-aldol **223** would be prepared from the *syn*-aldol reaction of α-chloro oxazolidin-2-one auxiliary **166** with acrolein **222**. Cyclopropyl *bis*-aldol **225** would be synthesised following the previously described directed cyclopropanation protocol using aldol **224** as a substrate. The target intermediate, *bis*-vinyl cyclopropane **227**, would then be

synthesised *via* the samarium(II) iodide mediated β-elimination reaction of **225**, and subsequent DIBAL-H mediated cleavage of the oxazolidin-2-one fragment. Cyclopropane dialdehyde **227** could then undergo further iterations for the synthesis of odd-numbered oligomeric cyclopropanes.

Therefore, α-chloroacetyl oxazolidin-2-one **166** was reacted under our standard *syn*-aldol conditions (dibutyl boron triflate, $^{i}Pr_2NEt$) with acrolein, to afford α-chloro *syn*-aldol **223** (**Scheme 2.4-25**). α-Chloro *syn*-aldol **223** was obtained in good yield, but with decreased diastereoselectivity when this *syn*-aldol reaction was allowed to warm to room temperature overnight in the usual manner. Under these conditions, the desired α-chloro-β-vinyl *syn*-aldol **223** was generated in 88% de and 82% yield, and in >95% de after purification by silica gel chromatography. Alternatively, the desired *syn*-aldol could be synthesised with a diastereomeric excess of >95% de, but with decreased yield, by maintaining the reaction temperature at -78°C for one hour before warming the reaction to 0°C, which resulted in *syn*-aldol **223** being isolated in a decreased 63% yield. The remaining mass balance from this second low temperature methodology comprised unreacted chiral auxiliary **166** and aldehyde **222**.



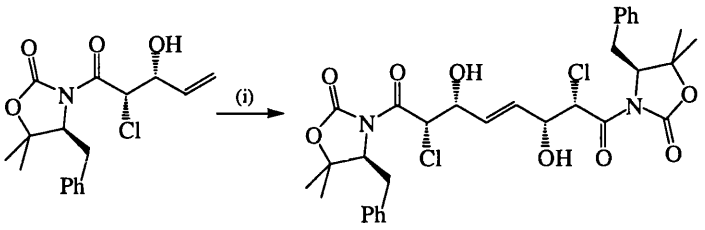
166 **223**

Reagents and conditions: (i) Dibutyl boron triflate, $^{i}Pr_2NEt$, CH_2Cl_2, 0°C, 1 hour, acrolein, -78 to RT; (ii) Dibutyl boron triflate, $^{i}Pr_2NEt$, CH_2Cl_2, 0°C, 1 hour, acrolein, -78°C, 1 hour then 0°C 1 hour.

Scheme 2.4-25 – *syn-Aldol reaction of acrolein*

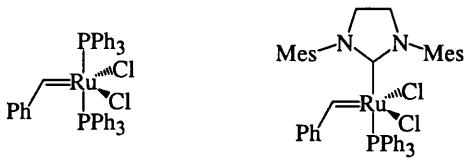
With the desired *syn*-aldol **223** in hand, an intermolecular metathesis reaction was then attempted (**Scheme 2.4-26**). First generation Grubb's catalyst showed no reactivity with this compound, despite increased reaction times, resulting in only starting *syn*-aldol **223** starting material being recovered. Changing to second generation Grubb's catalyst[162] afforded the desired (*E*)-unsaturated *bis*-aldol **224** in >95% de and in essentially quantitative yield. The (*E*)-configuration of **224** was

assumed from literature precedent,[163] and since no resonances corresponding to a (*Z*)-alkene were observed in the crude ^{1}H-NMR spectrum.



223 **224**

96% Yield
>95% de

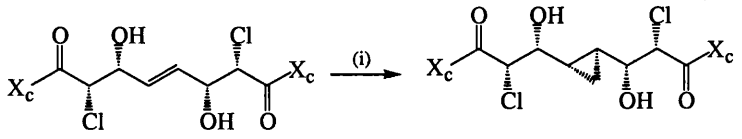


1st Generation Grubb's catalyst 2nd Generation Grubb's catalyst

Reagents and conditions: (i) 2nd generation Grubb's (5 mol%), CH_2Cl_2, reflux, 2 hours.

Scheme 2.4-26 – *Intermolecular metathesis reaction of α-chloro unsaturated syn-aldol*

This unsaturated *bis*-aldol **224** was then treated under our standard cyclopropanation conditions (Et_2Zn, CH_2I_2, see **Section 2.2.5**); however, the yield of cyclopropane aldol **225** was found to be disappointingly low (<5%). Increasing the reaction time and temperature of this directed cyclopropanation reaction was successful in affording a good yield of the cyclopropyl *syn-bis*-aldol **225** (**Scheme 2.4-27**).



224 **225**

X_c = SuperQuat

71% yield
81% de

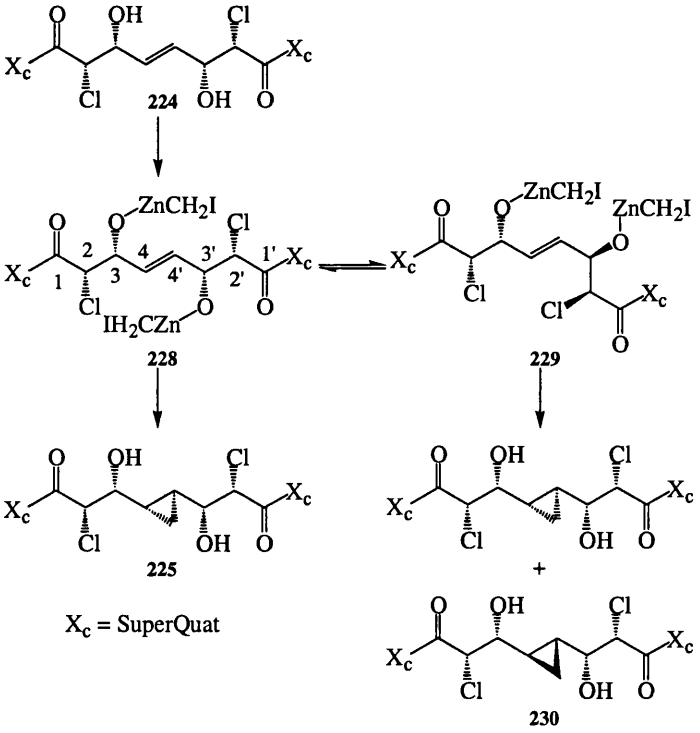
Reagents and conditions: (i) Et_2Zn (5 eq.), CH_2I_2 (5 eq.), CH_2Cl_2, -40 to RT overnight.

Scheme 2.4-27 – *Directed cyclopropanation of bis-aldol 224*

Analysis of the ^{1}H-NMR spectrum of the crude reaction product revealed that this hydroxyl directed cyclopropanation reaction had proceeded to afford the desired

cyclopropyl *bis*-aldol **225** in a non-optimised 81% de, which was purified by silica gel chromatography to afford the desired compound in >95% de and 71% yield. NOE-NMR experiments on the two diastereomers of cyclopropane aldol **225** proved inconclusive in assigning their configurations, presumably due to the conformational mobility of both diastereomers. Attempts to grow crystals of the major diastereomer for X-ray crystallographic studies were also unsuccessful. Therefore, the all *syn*-stereochemistry of major diastereomer **225** was assigned from literature precedent for this type of directed cyclopropanation reaction.[113]

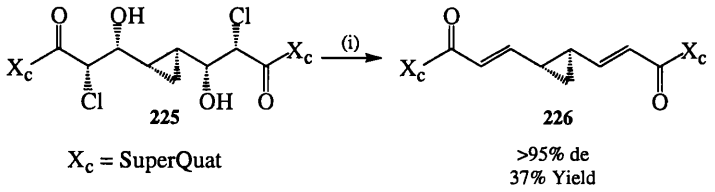
Due to the C_2 symmetry of the compound, both hydroxyl groups should direct the zinc to the same diastereotopic face of the olefin; however, they clearly cannot carry out this reaction simultaneously. Therefore, it was proposed that the reduction in rate and selectivity in the cyclopropanation reaction of *bis*-aldol substrate **224**, when compared to the cyclopropanation reaction of *mono*-aldol substrates, was possibly due to steric hindrance arising from the presence of a non-participating zinc alkoxide fragment in the cyclopropanation reaction (**Scheme 2.4-28**).



Scheme 2.4-28 – *Proposed mechanism for the reduction in facial selectivity of the directed cyclopropanation of bis-aldol 224*

Reaction of *bis*-aldol **224** with the cyclopropanating reagent has the potential to generate *bis*-zinc alkoxide intermediate **228**. This conformation results in a minimisation of $A^{1,3}$-strain with the α-chloro substituent, and should result in cyclopropanation of the olefin to afford the desired all *syn*-cyclopropyl aldol **225**. However, this conformation also results in two sterically hindered zinc alkoxides fragments being positioned in close proximity, which may generate $A^{1,4}$-strain that could be minimised by rotation around the C3'-C4' bond to afford an alternative conformational intermediate **229**. These two cyclopropanating species would then direct the cyclopropanation reaction to opposite diastereotopic faces of the olefin, with the C3-zinc-alkoxide fragment affording the *syn*-cyclopropane and the C3'-zinc-alkoxde fragment affording the *anti*-cyclopropane. From the diastereoselectivity of the reaction, it would appear that the major reactive conformer is *syn*-intermediate **228,** but that the relatively small differences in energy between the two conformers results in small amounts of the *anti*-conformer **230**, which leads to the observed loss in diastereocontrol under these reaction conditions.

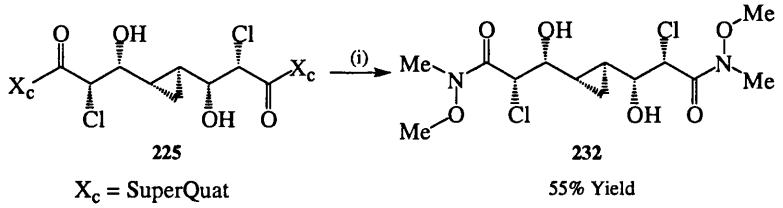
Cyclopropyl *bis*-aldol **225** was then treated with ten equivalents of samarium(II) iodide under our previously described conditions (**Scheme 2.4-29**). This tandem elimination reaction afforded the expected *bis*-alkene cyclopropyl substrate **226** in a disappointing 37% yield, though excellent (*E*)-diastereoselectivity (>95% de) for both β-elimination reactions was observed. The desired cyclopropyl diene **226** was purified simply *via* recrystallisation of the crude reaction product, but the by-product **231** of this *bis*-elimination reaction proved difficult to isolate, despite repeated attempts at chromatographic purification. The structure of *bis*-alkene cyclopropane **226** was assigned from consideration of its ^{1}H-NMR spectrum, due to the presence of a low field chemical shift at δ7.35 ppm for the α-protons of the conjugated alkene, which arises from the strong anisotropic deshielding effect of the benzyl group on the oxazolidin-2-one fragment. The *trans*-stereochemistry was assigned from literature precedent, and confirmed by the large alkene coupling constant of $J_{2,3}$ = 15 Hz. The molecular weight of the molecule was confirmed by the high-resolution mass spectrum, whilst the C_2-symmetry of **226** was evident from the ^{13}C-NMR spectrum that displayed only fifteen resonances.



Reagents and conditions: SmI_2 (10 eq.), THF, 2 hours.

Scheme 2.4-29 – *Double elimination reaction of cyclopropyl bis-aldol*

During our synthesis of *Grenadamide* **191** (**Section 2.4.5**), it had been observed that replacing the oxazolidin-2-one auxiliary fragment for an amide functionality had greatly improved the yield of the resultant β-elimination reaction. We therefore treated *bis*-aldol **225** with trimethylaluminium and *N,O*-dimethylhydroxylamine, which cleaved the oxazolidin-2-one fragment to afford a Weinreb *bis*-aldol amide **232**. (**Scheme 2.4-30**).[164]



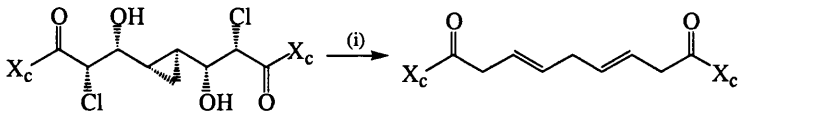
Reagents and conditions: (i) Me_3Al, MeNHOMe, THF, 0°C, 1 hour.

Scheme 2.4-30 – *Formation of Weinreb bis-aldol amide*

Unfortunately, treatment of **232** with samarium(II) iodide under the same conditions, failed to improve the yield of the β-elimination reaction, once again affording significant amounts of an unwanted by-product that was structurally related to **231** as indicated by examination of the crude ^{1}H-NMR spectrum.[165]

Examination of the impure ^{1}H-NMR spectrum of the by-product **231** (**Scheme 2.4-29**) from the *bis*-elimination reaction (**Appendix 4.3**) revealed no evidence of a cyclopropane ring, as indicated by the loss of the diagnostic high-field resonances corresponding to the cyclopropane protons. Resonances corresponding to a new non-conjugated double bond were evident, as established by a 2H multiplet at δ5.73 ppm and δ5.49 ppm respectively. We therefore tentatively proposed *bis*-alkene oxazolidin-

2-one substrate **231** as the major by-product in the β-elimination reaction of *bis*-aldol **225** (**Scheme 2.4-31**). The deshielding effect of the alkene functionality was seen to have shifted the α-proton downfield from δ5.82 ppm to δ6.93 ppm. A new doublet at δ3.78 ppm was assigned to the central methylene unit, deshielded by two alkene functionalities. Resonances corresponding to the oxazolidin-2-one fragment were still present, as observed for the characteristic peaks at δ4.17 ppm, δ2.91 ppm and δ2.24 ppm respectively. Finally, the presence of only fifteen resonances in the ^{13}C-NMR demonstrated that the molecule retained its C_2 symmetry, whilst the low-resolution mass spectrum revealed a molecular ion at 581 Da ($[M+Na]^+$) that confirmed the structure of **231**.



X_c = SuperQuat

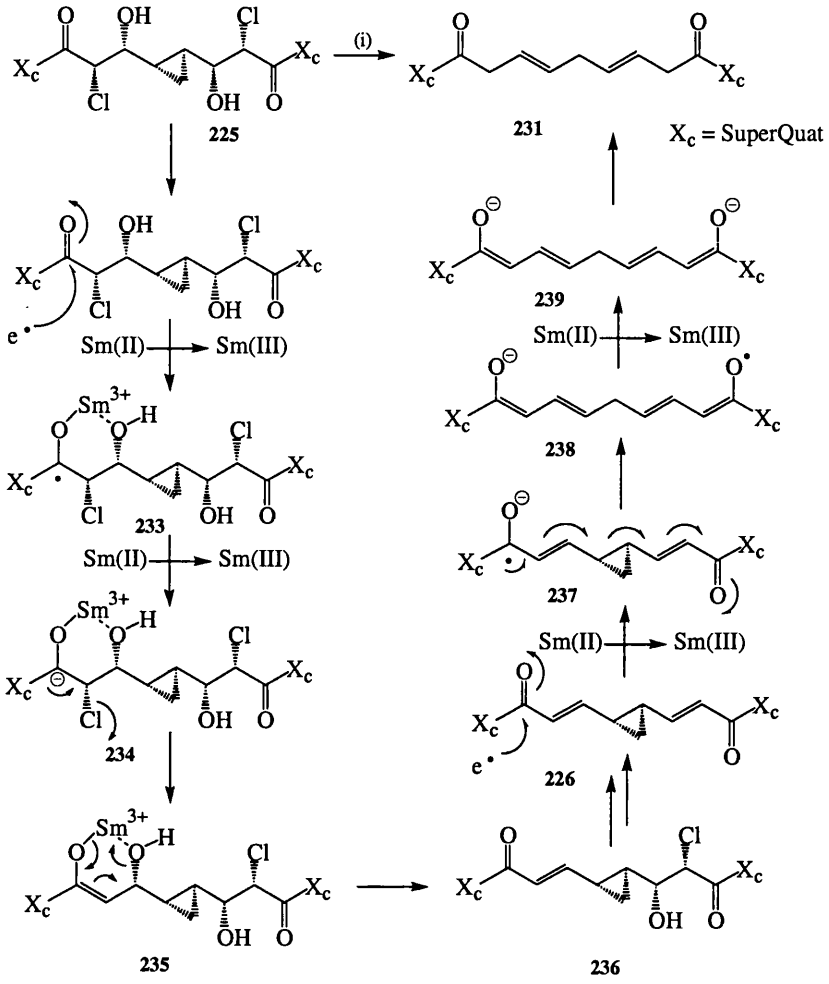
225 **231**

Reagents and conditions: (i) SmI_2 (10 eq.), THF, RT, 2 hours.

Scheme 2.4-31 – *Formation of by-product 231 from bis-elimination reaction*

In order to explain the formation of *bis*-alkene **231** it was proposed that the cyclopropane *bis*-aldol **225** undergoes a radical reduction of one of its exocyclic carbonyl groups to afford samarium(III) radical anion **233**, which is further reduced with a second equivalent of samarium(II) to afford anion **234**. Elimination of chloride is then followed by subsequent $E1_cb$ elimination of the β-hydroxyl group in the usual manner, to afford unsaturated intermediate **236**. This process is then repeated for the elimination of the second α-chloro-β-hydroxy motif of **236**, to afford the desired divinyl cyclopropane **226**. Due to the presence of excess of samarium(II) iodide used in this reaction however, divinyl cyclopropane **226** may then undergo further reduction of its exocyclic carbonyl, to afford radical anion intermediate **237**, which it is proposed then initiates a further elimination reaction of the cyclopropane ring to afford radical enolate **238**,[166] which can then be reduced to afford *bis*-enolate

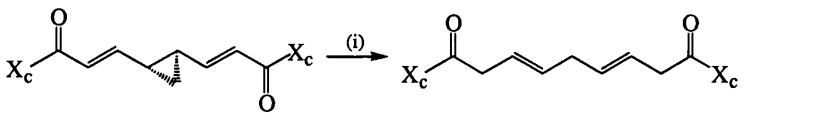
intermediate **239**. This product is then subsequently protonated during the work-up of this reaction to afford diene **231** as a competing by-product.[167]



Reagents and conditions: (i) SmI_2 (10 eq.), THF, RT, 1 hour.

Scheme 2.4-32 – *Proposed mechanism for elimination of cyclopropane motif*

Evidence for this mechanism was provided by treatment of divinyl cyclopropane **226** with samarium(II) iodide in THF for one hour, which resulted in formation of by-product **231** as determined by examination of the crude ^{1}H-NMR spectrum of the crude reaction product, thus demonstrating the intermediacy of divinyl cyclopropane **226** in the formation of by-product **231** (**Scheme 2.4-33**).

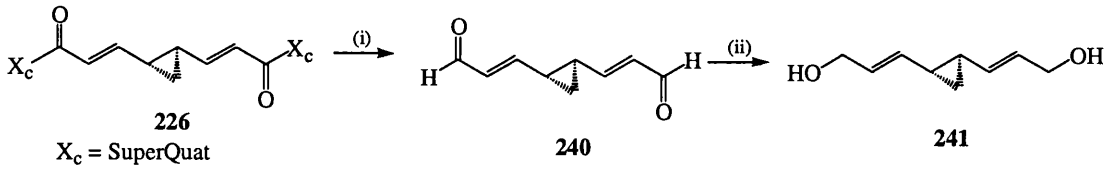


226 **231**

Reagents and conditions: (i) SmI_2 (3 eq.), THF, RT, 1 hour.

Scheme 2.4-33 – *Radical reduction of divinyl cyclopropane 226*

Divinyl cyclopropane **226** was then treated with DIBAL-H in dichloromethane at -78°C for 2 hours, before quenching the reaction at this temperature with aqueous saturated ammonium chloride solution and subsequently warming to room temperature over four hours. Examination of the crude ^{1}H-NMR revealed the presence of an aldehyde doublet at δ9.39 ppm, an alkene multiplet at δ6.21 ppm and a vinyl-cyclopropane multiplet at δ1.98 ppm, which were assigned as cyclopropane *bis*-α,β-unsaturated dialdehyde **240**. Due to the small scale of this reaction (10 mg of divinyl cyclopropane **226**), this dialdehyde **240** was not isolated but further reduced with sodium borohydride to afford cyclopropane *bis*-allylic alcohol **241**, whose spectroscopic data matched that previously described in the literature. (**Scheme 2.4-34**).[168] The stereochemistry of the cyclopropane fragment of **241** was confirmed as (*R*,*R*) by comparison of the specific rotation of this compound with known literature values ($[\alpha]_D^{25}$ = -105, $[\alpha]_D^{lit.}$ = -131).[169,170]



226 **240** **241**

Reagents and conditions: (i) DIBAL-H, CH_2Cl_2, -78°C, then $NH_4Cl_{(aq)}$; (ii) $NaBH_4$, THF, RT.

Scheme 2.4-34 – *Selective reduction of divinyl cyclopropane 226*

Methodology has therefore been developed to access the key intermediate, *bis*-α,β-unsaturated dialdehyde **240**, which it is proposed in the future will be used as a substrate for further iterations of our aldol/directed cyclopropanation/samarium(II)

elimination/DIBAL-H reduction strategy for the synthesis of odd numbered oligocyclopropanes.

2.4.9 Conclusion

It has been demonstrated that an alternative approach for using temporary stereocentres to relay chiral information can be applied to the asymmetric synthesis of *Grenadamide*. Key steps in this asymmetric synthesis include a highly diastereoselective *syn*-aldol and directed cyclopropanation reactions of α-chloroacetyl oxazolidin-2-one derived substrates, and the ability to carry out direct aminolysis on *N*-chloroacetyl-oxazolidin-2-one derived *syn*-aldols. Cleavage of the temporary stereocentre in this synthesis was achieved using highly diastereoselective samarium(II) iodide β-elimination methodology. To exploit the high diastereoselectivity of this reaction, a new strategy was proposed towards the synthesis of oligomeric cyclopropanes. Conditions were established for the asymmetric aldol reaction of *N*-chloroacetyl-oxazolidin-2-one **166** with acrolein, and the resultant *syn*-aldol was used in an intermolecular metathesis reaction. Conditions for cyclopropanation of the resulting *bis*-aldol **224** were described; whilst the subsequent samarium(II) β-elimination reaction was found to be only partially successful. Work is continuing within the SDB group towards further optimisation of this new methodology.

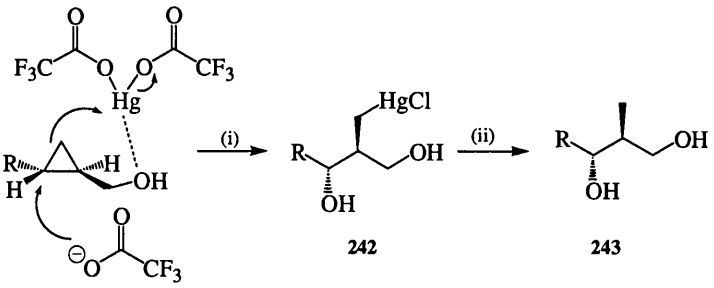
Chapter 2.5 Preliminary investigations into the asymmetric synthesis of chiral lactones as synthons for polypropionates

2.5.1 Introduction

This chapter describes attempts to exploit the excellent stereocontrol observed in the directed cyclopropanations of SuperQuat *syn*-aldols for electrophilic cleavage reactions of the cyclopropane ring using Hg^{2+} species for the asymmetric synthesis of polypropionate motifs in high de. An alternative strategy for the synthesis of highly functionalised *gamma*-lactones is also described that are easily accessed *via* directed epoxidation reactions on β-vinyl *syn*-aldol substrates.

2.5.2 A cyclopropanation approach towards the asymmetric synthesis of polypropionate sub-units

Polypropionate sub-units are key structural motifs found in a vast array of natural products that demonstrate a wide range of biological activity and as a consequence, they have been synthetic targets for many research groups.[171] Whilst most synthetic strategies rely on iterative aldol strategies to introduce contiguous stereocentres, recent work by Cossy and co-workers has demonstrated that oxymercuration of chiral cyclopropanes offers an alternative for constructing these structurally challenging motifs (**Scheme 2.5-1**).[172]

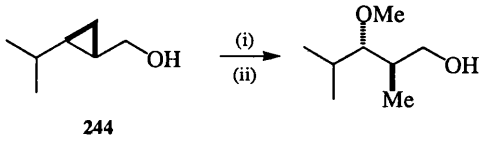


Reagents and conditions: (i) $Hg(OCOCF_3)_2$, CH_2Cl_2, then $NaCl_{(aq.)}$; (ii) reductive demercuration.

Scheme 2.5-1 – *Oxymercuration of cyclopropyl alcohols*

This reaction involves the stereoselective electrophilic ring opening of the cyclopropane ring through coordination with mercury(II) species, with the cyclopropane ring then being attacked by the trifluoroacetate anion to afford organomercury intermediate **242**. This reaction normally proceeds with essentially complete inversion at the cyclopropyl stereocentre and occurs in a highly regioselective manner *via* cleavage of the most electron rich carbon-carbon cyclopropyl bond. However, it is also likely that coordination of the mercury species to the allylic alcohol functionality plays a pivotal role in the regioselectivity of this reaction. Reductive demercuration of the organomercury intermediate **242** may then be carried out to afford the polypropionate sub-unit **243**.

The cyclopropane ring can also be cleaved by nucleophiles other than the trifluoroacetate counter-ion. For example, Barrett and co-workers have shown that the cyclopropane ring of **244** can be opened in the presence of methanol with excellent regioselectivity and complete inversion in configuration (**Scheme 2.5-2**).[173]



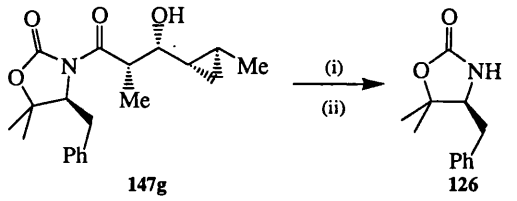
Reagents and conditions: (i) $Hg(OCOCF_3)_2$, MeOH, RT, then NaCl, H_2O; (ii) $LiAlH_4$, THF, 0°C.

Scheme 2.5-2 – *Intermolecular electrophilic ring opening of cyclopropanes*

The excellent stereocontrol observed for cyclopropanation of *syn*-aldols described previously in this thesis provided an excellent route to stereodefined cyclopropyl alcohols and as a consequence, it was decided to employ them as substrates for this mercury(II) mediated ring opening methodology.

2.5.3 The oxymercuration of cyclopropyl *syn*-aldols

Oxymercuration of α-methyl cyclopropyl *syn*-aldol **155b** *via* treatment with mercury(II) trifluoroacetate in dichloromethane at room temperature, followed by reductive demercurative workup with lithium aluminium hydride did not afford any organic-soluble ring opened products. Despite repeated attempts, only oxazolidin-2-one auxiliary **126** could be isolated from the reaction mixture (**Scheme 2.5-3**).



147g **126**

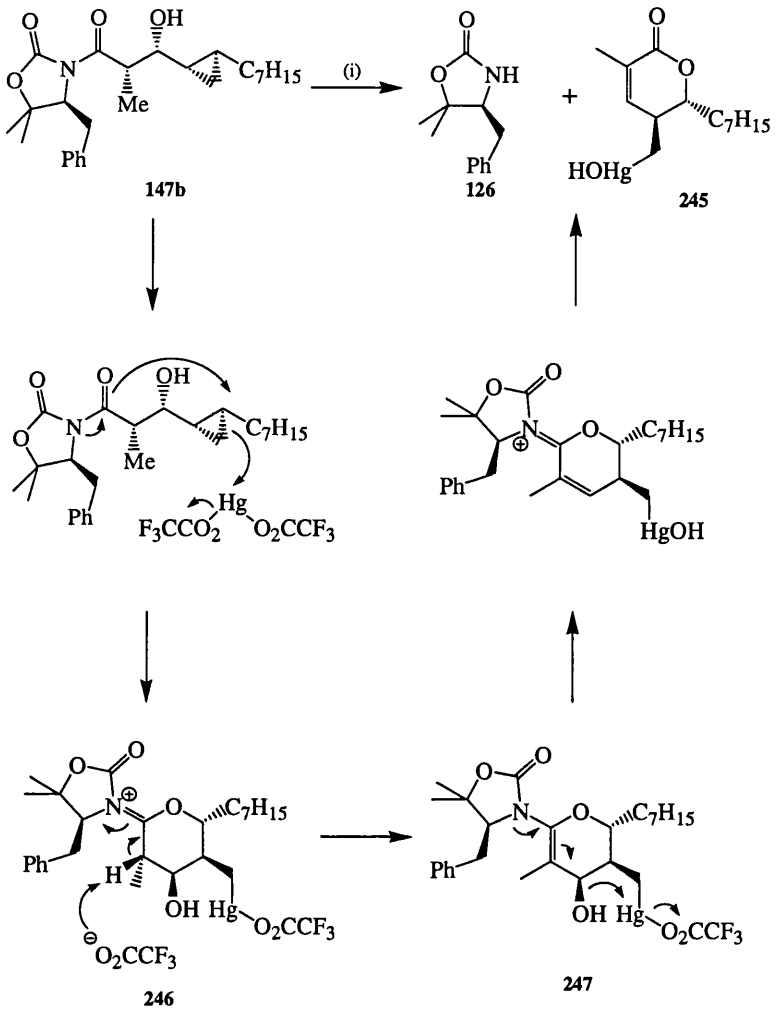
Only Product

Reagents and conditions: (i) $Hg(O_2CCF_3)$, CH_2Cl_2, RT, overnight, then $NaCl_{(aq.)}$; (ii) $LiAlH_4$, THF, 0°C, 1 hour.

Scheme 2.5-3 – *Oxymercuration/reductive demercuration of α-methyl cyclopropyl syn-aldol 155b*

Due to the difficulties in isolating the products of this reaction, oxymercuration of α-methyl cyclopropyl *syn*-aldol **147b** was therefore carried out in deuterated chloroform under the same conditions, such that any organomercury intermediates could be identified by ^{1}H-NMR spectroscopy (**Appendix 4.4**). Analysis of the ^{1}H-NMR spectrum of this reaction revealed that following hydrolysis the oxazolidin-2-one fragment had been cleaved from the compound, as indicated by the diagnostic peaks at δ3.96 ppm, δ2.84 ppm and δ2.67 ppm respectively. A new peak at δ6.34 ppm was characteristic of a conjugated alkene resonance, whilst the low field chemical shift of the multiplet at δ4.05 ppm indicated the close proximity of this resonance to an

electron withdrawing functionality. Therefore, the product of this oxymercuration reaction was tentatively assigned as the α,β-unsaturated lactone **245** (**Scheme 2.5-4**).

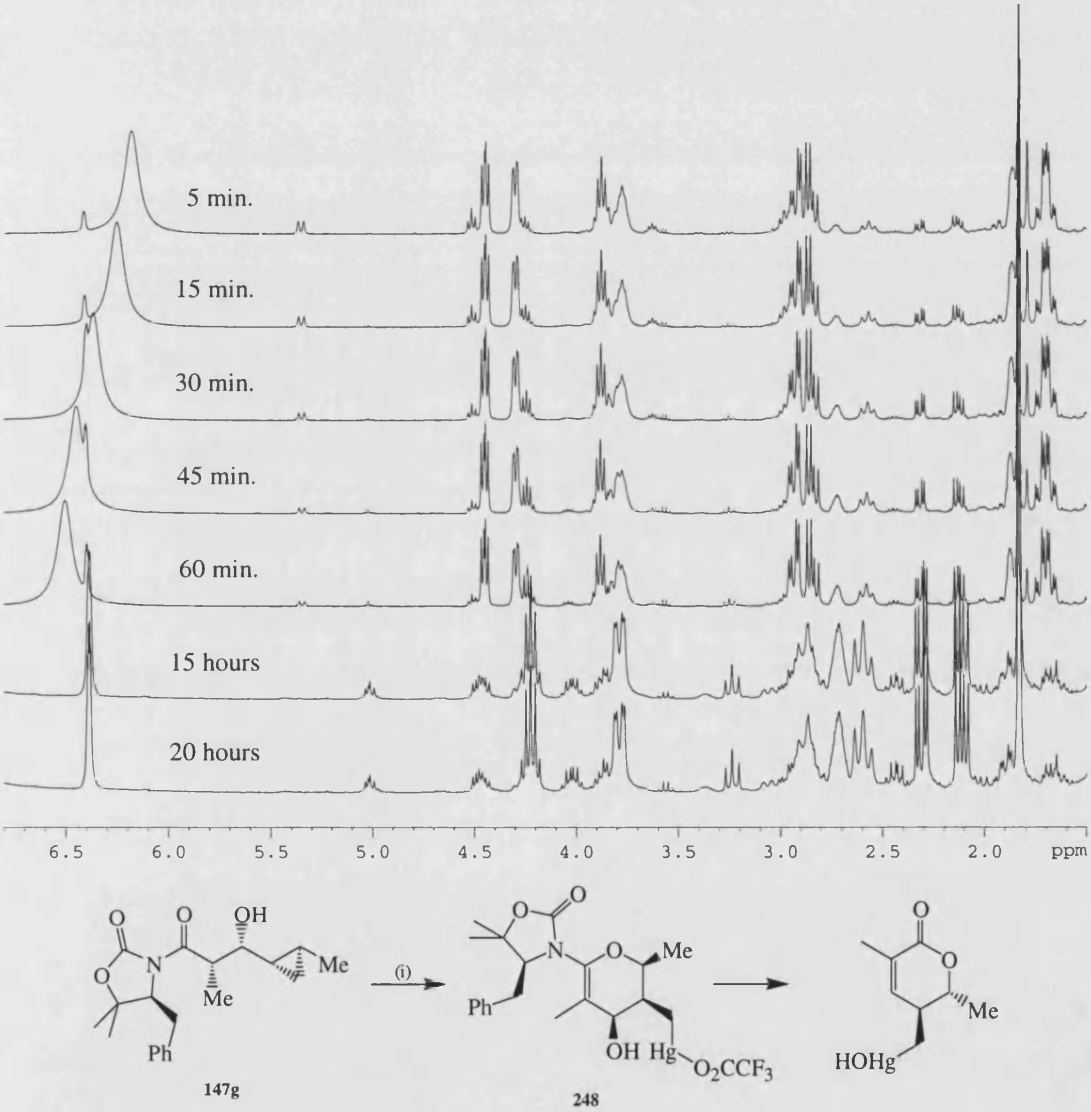


Reagents and conditions: (i) $Hg(O_2CCF_3)$, $CDCl_3$, RT, overnight, then $NaCl_{(aq.)}$.

Scheme 2.5-4 – *Synthesis of organomercurial derived α,β-unsaturated lactone*

The exocyclic carbonyl of *syn*-aldol **147b** acts as an intramolecular nucleophile to ring open the cyclopropane at its C-5 position, thus affording cyclic cationic intermediate **246**. The trifluoroacetate anion then deprotonates this cationic intermediate **246** at its α-position to initiate an $E1_cb$-type elimination to afford intermediate **247**, which is subsequently hydrolysed to afford α,β-unsaturated lactone **245**. Further ^{1}H-NMR spectroscopic studies of this oxymercuration reaction of α-

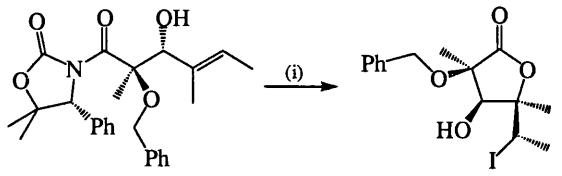
methyl cyclopropyl *syn*-aldol **147g** revealed that cleavage of the cyclopropane ring is extremely rapid (**Scheme 2.5-5**). Therefore, within five minutes of adding mercury(II) trifluoroacetate to the reaction mixture in deuterated chloroform at room temperature, no starting *syn*-aldol **147g** remained. $E1_cb$ elimination of the resulting intermediate **248** then occurs slowly over the following twenty hours, as indicated by the increasing intensity of the resonances at δ2.31 ppm and δ2.09 ppm that correspond to the mercuric diastereotopic methylene protons.



Reagents and conditions: (i) $Hg(O_2CCF_3)$, $CDCl_3$, RT, overnight.

Scheme 2.5-5 – *^{1}H-NMR spectroscopy study of oxymercuration reaction of α-methyl cyclopropyl syn-aldol **147g***

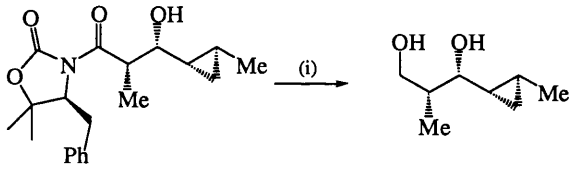
Kobayashi and co-workers have previously demonstrated that the oxazolidin-2-one fragment of aldol substrates could react as a nucleophile in an intramolecular fashion in their iodolactonisation of related β-vinyl *syn*-aldols substrates during their enantioselective total synthesis of *Citreoviral* (**Scheme 2.5-6**).[174]



Reagents and conditions: (i) I_2, $NaHCO_3$, acetonitrile/H_2O, RT.

Scheme 2.5-6 – *Iodolactonisation of unsaturated aldols*

To avoid this potential elimination reaction and due to the difficulties encountered in isolating the products of these reactions, it was decided to reductively cleave off the oxazolidin-2-one auxiliary fragment prior to carrying out the oxymercuration reaction. α-Methyl cyclopropyl *syn*-aldol **147g** was treated with lithium aluminium hydride to afford cyclopropyl diol **249** in an essentially quantitative 97% yield (**Scheme 2.5-7**).[175] No competing side products arising from endocyclic cleavage of the oxazolidin-2-one carbonyl were observed in this reaction.



147g **249**

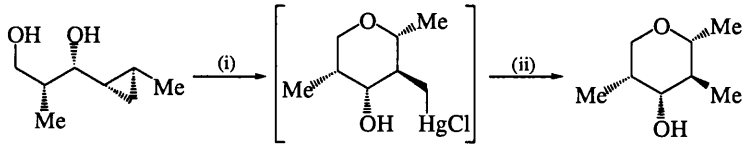
97% Yield

Reagents and conditions: (i) $LiAlH_4$, THF, 0°C, 2 hours.

Scheme 2.5-7 – *Reductive cleavage of oxazolidin-2-one auxiliary*

Cyclopropyl diol **249** was then treated under our standard oxymercuration conditions ($Hg(O_2CCF_3)_2$, CH_2Cl_2), which resulted in intramolecular nucleophilic cleavage of the cyclopropane ring by the primary alcohol functionality of **249** to afford organomercury intermediate **250**, which was not characterised further due to its

potential toxicity. Organomercurial intermediate **250** was then subjected to radical demercuration *via* treatment with tributyltin hydride and catalytic AIBN, to afford (2*R*,3*S*,4*R*,5*R*)-tetrahydro-2,3,5-trimethyl-2H-pyran-4-ol **251** in 91% yield. The structure of pyran **251** was confirmed by examination of its COSY spectrum and its stereochemistry assigned from literature precedent for this type of cyclopropane ring opening reaction (**Scheme 2.5-8**).[176, 177]



249 **250** **251**

91% Yield

Reagents and conditions: (i) $Hg(OCOCF_3)_2$, CH_2Cl_2, RT, 2 hours, then NaCl, H_2O, 2 hours; (ii) Bu_3SnH (4 eq.), AIBN, THF, RT, 4 hours, then NaF, H_2O.

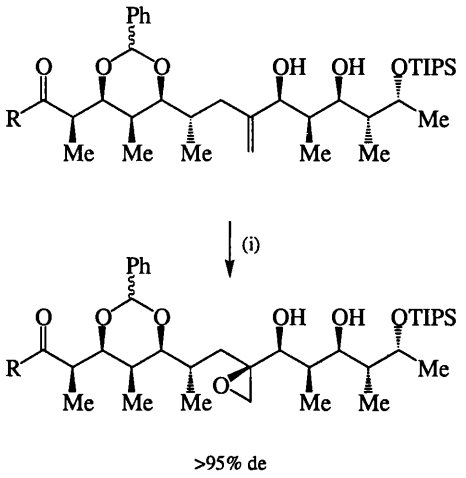
Scheme 2.5-8 – *Intramolecular cyclisation of cyclopropyl diol*

Therefore, the potential of this new methodology for the asymmetric synthesis of chiral lactones and polypropionate sub-units has been demonstrated and work to develop this methodology for natural product synthesis is currently underway with the SDB group.

2.5.4 The directed epoxidation of aldol substrates and the synthesis of *gamma*-lactones

Having demonstrated the utility of the directed cyclopropanation of chiral *syn*-aldols derived from *N*-acyl-oxazolidin-2-ones, a preliminary investigation was then carried out into an alternative directed reaction on our β-vinyl *syn*-aldol substrates. The most widely exploited substrate directable transformation reported to date has been the hydroxyl directed epoxidation of chiral allylic alcohols. For example, Evans and co-workers exploited this reaction for the synthesis of macrolide antibiotics with

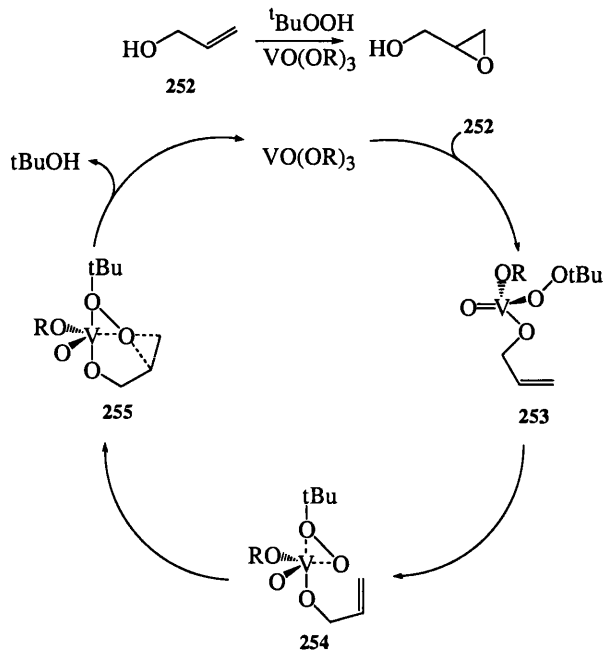
excellent levels of diastereocontrol, despite the presence of many surrounding stereocentres that had the potential to influence the outcome of this reaction (**Scheme 2.5-9**).[178]



Reagents and conditions: (i) $VO(acac)_2$, ^tBuOOH, benzene, RT.

Scheme 2.5-9 – *Hydroxyl directed epoxidation for the synthesis of macrolide antibiotics*

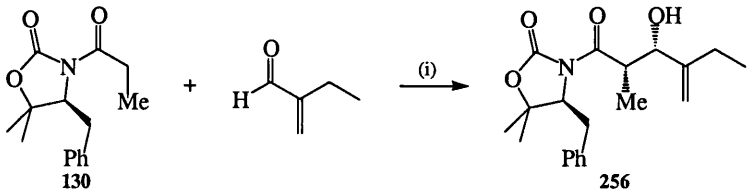
In the three step-catalytic cycle described in **Scheme 2.5-10**,[179] the allylic alcohol **252** first coordinates to the vanadium complex to afford intermediate **253** with displacement of an alkoxide ligand. Peroxide then binds to the metal centre with displacement of a second alkoxide ligand to afford intermediate **254**. An oxygen atom of **255** is then delivered to the olefin, regenerating the active site on the metal centre, which completes the catalytic cycle. The diastereoselectivity of these types of allylic epoxidation reaction arises from minimisation of $A^{1,3}$-strain in the transition state, as previously discussed in this thesis for the directed cyclopropanation reaction (**Scheme 2.2-7**).



Scheme 2.5-10 – *Proposed mechanism for the vanadium catalysed epoxidation of allylic alcohols*

2.5.5 Epoxidation of 1,1-disubstituted unsaturated *syn*-aldol

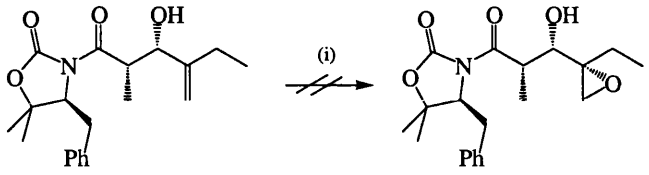
1,1-Disubstituted unsaturated *syn*-aldol **256** was synthesised *via* aldol reaction between the boron enolate of (*S*)-*N*-propionyl-4-benzyl-oxazolidin-2-one **130** and 2-ethylacrolein to afford *syn*-aldol **256** in 81% yield and >95% de (**Scheme 2.5-11**).



Reagents and conditions: 9BBN-OTf, $^{i}Pr_2NEt$, CH_2Cl_2, 0°C, 1 hour, 2-ethylacrolein, -78°C to RT, overnight.

Scheme 2.5-11 – *Synthesis of syn-aldol containing a 1,1- disubstituted alkene functionality*

1,1-Disubstituted unsaturated *syn*-aldol **256** was then treated with 10 mol% $VO(acac)_2$ and one equivalent of *tert*-butyl hydrogen peroxide in benzene at room temperature, followed by aqueous workup (**Scheme 2.5-12**).

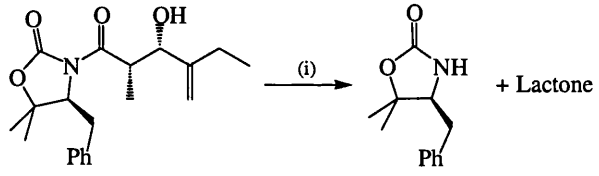


256 **257**

Reagents and conditions: (i) 10 mol% $VO(acac)_2$, tert-butyl hydrogen peroxide, benzene, RT then water

Scheme 2.5-12 – *Directed epoxidation of syn-aldol substrate 256*

Examination of the crude ^{1}H-NMR spectrum of this reaction revealed that treatment of **256** under these epoxidation conditions had failed to produce any of the desired epoxy aldol **257**. Instead, this ^{1}H-NMR spectrum revealed the presence of only clean oxazolidin-2-one **126**, with no products derived from the *syn*-aldol chain. However, subsequent saturation of the aqueous layer generated during work-up with sodium chloride followed by extraction with ethyl acetate resulted in isolation of a lactone product. (**Scheme 2.5-13**).



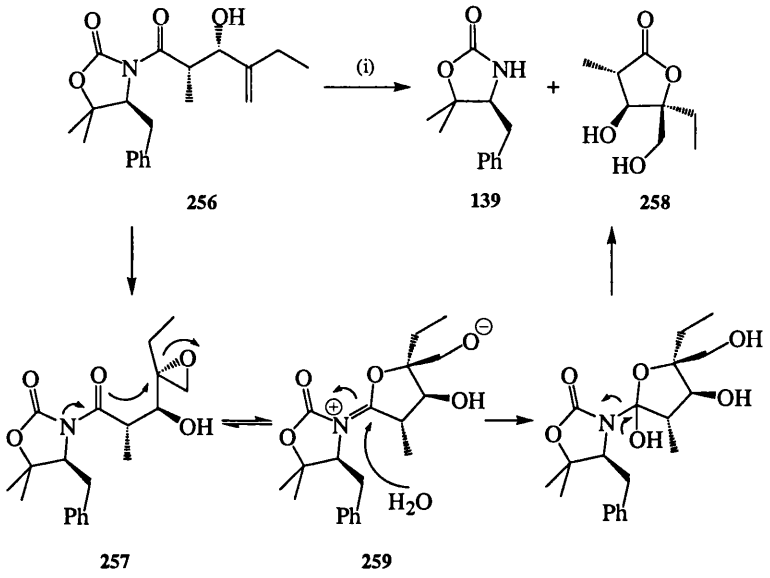
256 **126**
85% yield

Reagents and conditions: (i) 10 mol% $VO(acac)_2$, tert-butyl hydrogen peroxide, benzene, RT

Scheme 2.5-13 – *Lactone formation from β-vinyl syn-aldol* **256**

The proposed mechanism for the formation of hydroxyl *gamma*-lactone **258** is shown in **Scheme 2.5-14**. The hydroxyl directed epoxidation occurs on the olefin to afford epoxy *syn*-aldol **257**, whose absolute configuration was assigned from literature precedent.[178] As observed for the cyclopropane ring-opening reactions described earlier in this chapter, the exocyclic carbonyl then acts as a nucleophile to ring-open

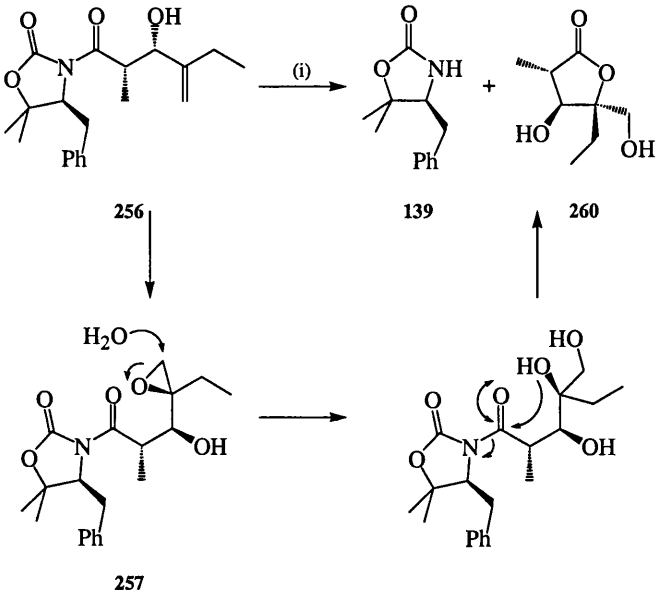
the epoxide in an intramolecular manner with inversion of configuration to afford iminium intermediate **259**. Treatment of this intermediate with water hydrolyses the resultant iminium species, cleaving the oxazolidin-2-one fragment and releasing the hydroxy *gamma*-lactone **258** in 78% yield and >95% de after purification by recrystallisation.



Reagents and conditions: (i) 10 mol% $VO(acac)_2$, tert-butyl hydrogen peroxide, benzene, RT.

Scheme 2.5-14 – *Proposed mechanism for the intramolecular cyclisation of epoxy aldol*

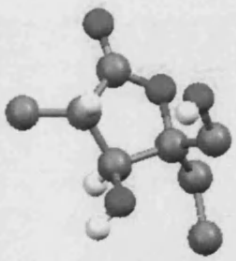
This intramolecular cyclisation pathway appeared the most likely mechanism; however, it was also possible that direct hydrolysis of the epoxide by water might have resulted in lactone formation occurring. In this case, water would attack the less sterically hindered end of the epoxide to afford diol **257**, which would then cyclise on the exocyclic carbonyl, with the oxazolidin-2-one fragment being cleaved as a leaving group (**Scheme 2.5-15**).

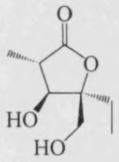


Reagents and conditions: (i) 10 mol% $VO(acac)_2$, tert-butyl hydrogen peroxide, benzene, RT.

Scheme 2.5-15 – *Alternative mechanism for formation of gamma-lactone* ***260***

This alternative mechanism would result in the opposite configuration at the quaternary centre of the *gamma*-lactone **260** to that arising from the intramolecular mechanism shown in **Scheme 2.5-14**. Therefore, in order to confirm which reaction mechanism was operating, the stereochemistry of the lactone's quaternary stereocentre needed to be confirmed. It is notoriously difficult to determine the configuration of stereocentres within *gamma*-lactones from analysis of coupling constants and as a consequence, an X-ray crystal structure of **258** was obtained (**Figure 2.5-1**). This established the (*S*) absolute configuration of the tertiary centre of lactone **258**, which confirmed a ring-opening mechanism involving inversion by S_n2 intramolecular nucleophilic attack by the exocyclic carbonyl of intermediate **259**.

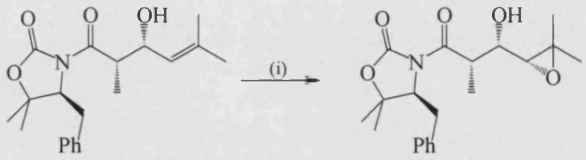




Colour code: grey, C = Grey, O = Red, H = White; selected hydrogens omitted for clarity.

Figure 2.5-1 – *X-Ray crystal structure of gamma-lactone* ***258***

In contrast, epoxidation of the allylic alcohol functionality of α-methyl *syn*-aldol **156a** under the same conditions revealed that this epoxy aldol **261** had greatly increased stability to lactonisation (**Scheme 2.5-16**). The stereochemistry of this epoxide was assumed from literature precedent and by minimisation of $A^{1,3}$-strain in the transition state. This resulted in assignment of the all *syn*-stereochemistry of epoxy-aldol **261** in a non-optimised 78% de, which was purified to >95% de and in 73% yield by recrystallisation.[180]

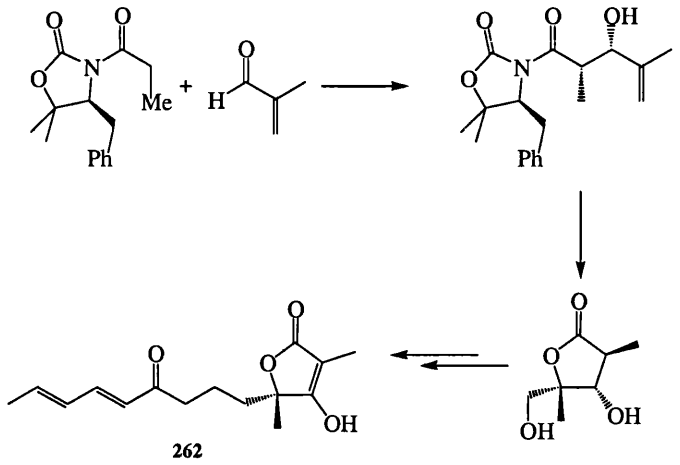


147h → **261**
73% Yield
78% de

Reagents and conditions: (i) 10 mol% $VO(acac)_2$, tert-butyl hydrogen peroxide, benzene, RT then water saturated with NaCl and extracted with EtOAc

Scheme 2.5-16 – *Formation of stable epoxy-aldol*

This epoxidation methodology is currently being applied within the SDB group to the asymmetric synthesis of the mycotoxin (-)-*Vertinolide* **262** as a further example of our *temporary stereocentre* methodology in synthesis (**Scheme 2.5-17**).[181]



Scheme 2.5-17 – *Proposed synthesis of (-)-Vertinolide*

2.5.6 Conclusion

It has been demonstrated that cyclopropane *syn*-aldols derived from *N*-acyl-oxazolidin-2-ones undergo a highly diastereoselective and regioselective electrophilic ring-opening reaction that may be used in the synthesis of pyrans. Directed epoxidation reactions on these types of *syn*-aldol products have also been carried out in high yield and de that resulted in a novel ring-opening/cyclisation reaction for the asymmetric synthesis of hydroxy *gamma*-lactones.

3 Experimental

General procedures

Infrared spectra (4000 cm^{-1} to 0 cm^{-1}) were recorded from thin films or as potassium bromide discs on a Perkin Elmer (1600) FT spectrometer with internal calibration. Only selected peaks are quoted in ν cm^{-1}.

All capillary melting points were measured using Buchi 535 melting point apparatus. The readings were taken from a mercury in glass thermometer and are reported uncorrected as the meniscus point, rounded to the nearest 1°C with a heating ramp of 0.5°C.

Proton magnetic resonance spectra were recorded at 300.22 MHz on Bruker Avance 300 spectrometer. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddt, doublet of doublet of triplets; qd, quartet of doublets; ddd, doublet of doublet of doublets; m, multiplet. Chemical shifts (δH) are quoted in parts per million and are referenced to the residual solvent peak. The multiplicities and general assignments of spectroscopic data are denoted as: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of doublet of triplets (ddt), quartet of doublets (qd), multiplet (m), apparent (app.), obscured (obs.), broad and aromatic (Ph). Coupling constants (J) are quoted to the nearest 0.5 Hz.

Carbon magnetic resonance spectra were recorded at 75.5 MHz on a Bruker Avance 300 spectrometer. Chemical shifts (δC) are quoted in parts per million and are referenced to the residual solvent peak. Coupling constants (J) are quoted to the nearest 0.5 Hz and are denoted as above.

Mass spectra were recorded at the EPSRC National Mass Spectrometry Service Centre, Swansea. Electron impact (EI) and chemical ionisation (CI) analyses were

performed in the positive ionisation mode. For low-resolution measurements, ammonia was used as a CI reagent gas on a Micromass Quattro II triple quadropole instrument. For high resolution measurements, heptacosa (perfluorotributylamine) was used as the EI and CI reference compound, and were performed on the Finnigan MAT900 high resolution double focusing mass spectrometer with tandem ion tap or on a MAT95 high resolution double focusing mass spectrometer. Both low and high-resolution fast atom bombardment (FAB) analyses were performed, in positive or negative ionisation mode, on either a Finnigan MAT900 or a MAT95, using 3-nitrobenzyl alcohol (NOBA) as the matrix liquid.

Single crystal X-ray diffraction data was collected on a Nonius Kappa CCD machine. Structure determination and refinement were achieved using SHELX suite of programmes; drawings were produced using ORTEX or MERCURY.

Analytical thin layer chromatography was carried out using commercially available glass-backed plates coated with Merck Kieselgel 60 GF_{254} or aluminium backed plates coated with coated with Merck or Macherey-Nagel G/UV_{254}. Plates were visualised under UV light (at 254 nm) or by staining with potassium permangenate, phosphomolybdic acid or *o*-bromocreosol, followed by heating. Flash chromatography was carried out using Merck 60 H silica gel (35-70 μm). Samples were either pre-absorbed onto silica or loaded as saturated solutions in an appropriate solvent.

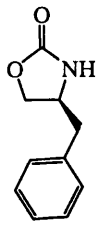
Anhydrous tetrahydofuran and diethyl ether were obtained by distillation from sodium benzophenone ketyl radical under nitrogen. Anhydrous toluene was obtained by distillation from sodium wire under nitrogen. Anhydrous dichloromethane was obtained by distillation from calcium hydride under nitrogen. Commercially available anhydrous benzene and acetone were dried over 3Å molecular sieves for two days prior to use. Were relevant, solvents were degassed under nitrogen using standard freeze/thaw techniques. Petrol refers to the fraction of petroleum ether boiling at 40°C-60°C. Ether refers to diethyl ether. Solvents were evaporated on a Buchi Rotorvapor.

All commercially available compounds were used as obtained from the chemical suppliers.

Reactions requiring anhydrous conditions were performed under nitrogen in flame-dried apparatus. All temperatures that are quoted are external.

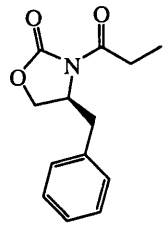
Chapter 3.1 General procedures for the synthesis of chiral 1,3-oxazinane-2,4-diones

3.1.1 (*S*)-4-Benzyloxazolidin-2-one (Evans' Auxiliary) 113



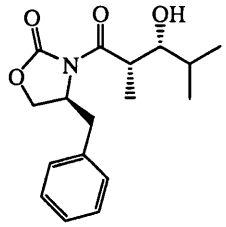
The preparation of the title compound was adapted from the previously published procedure.[182] Diethyl carbonate (2 equivalents) was added to a (*S*)-phenylalaninol, (1 equivalent) immediately followed by the addition sodium ethoxide in one portion in a three-necked flask fitted with standard distillation equipment, under nitrogen. The reaction was stirred for 10 minutes, then heated to 125°C for eight hours, or until ethanol ceased to distil from the reaction. The reaction was quenched with saturated aqueous ammonium chloride solution (5 cm^3), extracted with ether (3 x 20 cm^3), washed with brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. Purification *via* recrystallisation (Et_2O, hexane) gave **113** as a white solid in 73% yield, which matched the previously published data for this compound;[183] R_f (CH_2Cl_2) = 0.21; mp = 83-85°C (Et_2O, Hexane); $[\alpha]_D^{25}$ = -56 (c = 0.45, $CHCl_3$); δH (300 MHz, $CDCl_3$) 7.39-7.14 (5H, m, Ph), 5.70 (1H, broad s, NH), 4.45 (1H, m, CHN), 4.18-4.03 (2H, m, OCH_2), 2.88 (2H, app. d, J = 6.5 Hz, CH_2Ph); δC (75MHz, $CDCl_3$) 159.1, 136.3, 129.4, 129.7, 27.7, 70.1, 54.2, 41.9; IR (KBr / cm^{-1}) 3292 (broad N-H), 1752 (C=O).

3.1.2 (*S*)-4-Benzyl-3-propionyloxazolidin-2-one 88



n-BuLi (1.01 equivalents, 2.5 mol dm^{-3} solution in hexane) was added to a solution of (*S*)-4-benzyloxazolidin-2-one **113** (1 equivalent) in THF (20 cm^3) at -78°C under nitrogen and stirred for 30 minutes. Propionyl chloride (1.1 equivalents) was then added dropwise to the stirred solution over approximately five minutes and stirred for a further two hours, during which time the reaction was allowed to warm to 0°C. The reaction was then quenched with aqueous saturated ammonium chloride solution (5 cm^3) and allowed to room temperature, diluted with ether (10 cm^3), washed with aqueous saturated sodium hydrogen carbonate solution, sufficient to dissolve the white precipitate, extracted with ethyl acetate (3 x 20 cm^3), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. Purification *via* recrystallisation (Et_2O, hexane) gave **88** as a white solid in 75% yield, which matched the previously published data for this compound;[184] R_f (CH_2Cl_2) = 0.74; mp = 37-39°C (Et_2O, Hexane); $[\alpha]_D^{25}$ = +81 (c = 0.59, $CHCl_3$); δH (300 MHz, $CDCl_3$) 7.37-7.18 (5H, m, Ph), 4.67 (1H, app. ddd, J = 13.0 Hz, 7.0 Hz and 3.5 Hz, CHN), 4.24-4.14 (2H, m, OCH_2), 3.30 (1H, dd, J = 13.0 Hz and 3.0 Hz, CH_AH_BPh), 3.07-2.85 (2H, m, CH_2CH_3), 2.77 (1H, dd, J = 13.0 Hz and 10.0 Hz, CH_AH_BPh), 1.21 (3H, t, J = 7.5 Hz, CH_3); δC (75MHz, $CDCl_3$) 174.5, 153.9, 135.7, 129.8, 129.4, 127.8, 66.6, 55.6, 38.3, 29.6, 8.7; IR (KBr / cm^{-1}) 1783 ($C=O_{ox}$), 1702 (C=O).

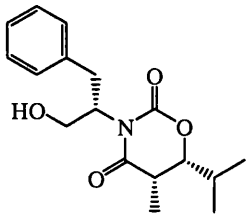
3.1.3 (*S*)-4-Benzyl-3-((2*S*,3*R*)-3-hydroxy-2,4-dimethyl-pentanoyl)-oxazolidin-2-one 114



9BBN-OTf (1.1 equivalents, 0.5 mol dm^{-3} solution in hexane) was added dropwise to a stirred solution of (*S*)-4-benzyl-3-propionyloxazolidin-2-one **88** (1 equivalent) in dry dichloromethane at 0°C, under nitrogen. After 30 minutes, diisopropylethylamine (1.2 equivalents) was added dropwise and the resulting solution stirred for a further 30 minutes. The solution was cooled to -78°C and isobutyraldehyde (1.1 equivalents) was added dropwise. The reaction was stirred at this temperature for 1 hour and then warmed to 0°C and stirred for one further hour. The reaction was quenched with Na_2PO_4/NaH_2PO_4 buffer solution (pH7, 10 cm^3), and stirred for 10 minutes before the addition of 2:1 methanol-hydrogen peroxide solution (30%, 10 cm^3) and stirred for 2 hours. The mixture was extracted with dichloromethane (3 × 20 cm^3), washed with aqueous saturated sodium hydrogen carbonate solution (10 cm^3), brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. The relative and absolute stereochemistry was assumed as drawn from literature precedent and from the small α-proton coupling constant (2.5 Hz). The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **114** as a yellow oil in 85% yield, which matched the previously published data for this compound;[185] R_f (CH_2Cl_2) = 0.31; $[\alpha]_D^{25}$ = +36 (c = 0.56, $CHCl_3$); δH (300 MHz, $CDCl_3$) 7.38-7.18 (5H, m, Ph), 4.70 (1H, app. ddt, J = 9.5 Hz, 7.0 Hz, and 3.5 Hz, CHN), 4.27-4.17 (2H, m, CH_2O), 3.96 (1H, qd, J = 7.0 Hz and 2.5 Hz, COCH), 3.54 (1H, dd, J = 8.5 Hz and 2.5 Hz, C*H*OH), 3.26 (1H, dd, J = 13.5 Hz and 3.5 Hz, CH_AH_BPh), 2.79 (1H, dd, J = 13.5 Hz and 9.5 Hz, CH_AH_BPh), 1.72 (1H, m, isopropyl-CH), 1.52 (1H, broad s, OH), 1.24 (3H, d, J = 7.0 Hz, CH_3CH), 1.04 (3H, d, J = 6.5 Hz, isopropyl-CH_3), 0.90 (3H, d, J = 6.5 Hz, isopropyl-CH_3); δC (75MHz,

$CDCl_3$); 178.2, 155.3, 135.5, 129.8, 129.4, 127.8, 77.1, 66.6, 55.6, 40.1, 38.2, 35.1, 19.7, 19.3, 10.4; IR (Film / cm^{-1}) 3538 (broad O-H), 1779 ($C=O_{ox}$), 1694 (C=O).

3.1.4 (5*S*,6*R*)-3-((*S*)-1-Hydroxy-3-phenylpropan-2-yl)-6-isopropyl-5-methyl-1,3-oxazinane-2,4-dione 115

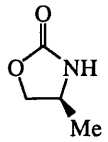


Diethyl zinc (10 mol%, 1 mol dm^{-3} solution in dichloromethane) was added dropwise to a solution (*S*)-4-Benzyl-3-((2*S*,3*R*)-3-hydroxy-2,4-dimethyl-pentanoyl)-oxazolidin-2-one **114** in dry dichloromethane at room temperature under nitrogen, and stirred for 1 hour. The reaction was quenched with saturated aqueous sodium sulfite solution (5 cm^3) and hydrochloric acid (1 mol dm^{-3} solution in water), sufficient to dissolve the white precipitate. Extracted with dichloromethane (3 x 20 cm^3), washed with saturated sodium hydrogen carbonate solution (10 cm^3), brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **115** as a yellow oil in 91% yield; R_f (CH_2Cl_2) = 0.32; $[\alpha]_D^{25}$ = -13 (c = 1.37, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.24-7.09 (5H, m, Ph), 5.02 (1H, app. ddt, J = 14.0 Hz, 7.0 Hz and 3.5 Hz, CHN), 4.00 (1H, dd, J = 11.5 Hz and 7.0 Hz, CH_AH_BOH), 3.82 (1H, dd, J = 11.5 Hz and 3.5 Hz, CH_AH_BOH), 3.20-3.06 (2H, obs. dd and m, J = 14.0 Hz and 10.5 Hz, CH_AH_BPh and OCH), 3.00 (1H, dd, J = 14.0 Hz and 6.5 Hz, CH_AH_BPh), 2.71 (1H, broad s, OH), 2.51 (1H, qd, J = 7.5 Hz and 2.5 Hz, $CHCH_3$), 1.74 (1H, m, isopropyl-CH), 0.99 (3H, d, J = 7.5 Hz, CH_3CH), 0.95 (3H, d, J = 7.0 Hz, isopropyl-CH_3), 0.68 (3H, d, J = 7.0 Hz, isopropyl-CH_3); δC (75MHz, $CDCl_3$) 174.2, 152.5, 137.4, 129.6, 128.9, 127.1, 85.4, 64.0, 56.6, 38.8, 33.9, 28.3, 19.4, 17.7,

9.3; IR (Film / cm^{-1}) 3441 (broad O-H), 1751 ($C=O_{ox}$), 1694 (C=O); HRMS : m/z (ES) $[M+H]^+$ requires 306.1700, found 306.1699.

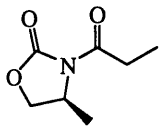
Chapter 3.2 General procedures for the asymmetric synthesis of *Semiplenamide C*

3.2.1 (*S*)-4-Methyloxazolidin-2-one 120



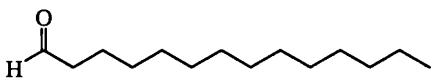
The preparation of the title compound was adapted from the previously published procedure.[182] Diethyl carbonate (2 equivalents) was added to (*S*)-alaninol (1 equivalent), immediately followed by the addition sodium ethoxide in one portion to a three-necked flask fitted with standard distillation equipment, under nitrogen. The reaction stirred for 10 minutes then heated to 125°C for eight hours, or until ethanol ceased to distil from the reaction. The reaction was quenched with saturated aqueous ammonium chloride solution (5 cm^3), extracted with ether (3 x 20 cm^3), washed with brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. Purification *via* recrystallisation (Et_2O, hexane) gave **120** as a white solid in 85% yield, which matched the previously published data for this compound;[186] R_f (CH_2Cl_2) = 0.69; mp = 42-44°C (Et_2O/Hexane) $[\alpha]_D^{25}$ = +11 (c = 1.32, $CHCl_3$) δH (300 MHz, $CDCl_3$) 6.53 (1H, broad s, NH), 4.47 (1H, m, C*H*CH_3), 3.96 (1H, m, OC*H*$_A$H$_B$), 3.89 (1H, dd, J = 8.5 Hz and 6.5 Hz, OCH$_A$*H*$_B$), 1.24 (3H, d, J = 6.0 Hz, C*H*$_3$CH); δC (75MHz, $CDCl_3$) 161.1, 72.6, 49.2, 21.5; IR (KBr / cm^{-1}) 3256 (broad N-H), 1745 (C=O).

3.2.2 (*S*)-4-methyl-3-propionyloxazolidin-2-one 121



n-BuLi (1.01 equivalents, 2.5 mol dm^{-3} solution in hexane) was added to a solution of (*S*)-4-methyloxazolidin-2-one **120** (1 equivalent) in THF (20 cm^3) at -78°C under nitrogen and stirred for 30 minutes. Propionyl chloride (1.1 equivalents) was then added dropwise to the stirred solution over approximately 5 minutes and stirred for a further two hours, during which time the reaction was allowed to warm to 0°C. The reaction was quenched with aqueous saturated ammonium chloride solution (5 cm^3) and allowed to warm to room temperature, diluted with ether (10 cm^3), washed with aqueous saturated sodium hydrogen carbonate solution, sufficient to dissolve the white precipitate, extracted with ethyl acetate (3 x 20 cm^3), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. Purification by column chromatography (SiO_2, CH_2Cl_2), gave **121** as a yellow oil in 78% yield, R_f (CH_2Cl_2) = 0.69; $[\alpha]_D^{25}$ = +81 (c = 1.21, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 4.55 (1H, m, CHN), 4.41 (1H, app. t, J = 8.5 Hz, OCH_AH_B), 3.97 (1H, dd, J = 8.5 Hz and 3.0 Hz, OCH_AH_B), 2.95-2.86 (2H, app. td, J = 7.0 Hz and 2.5 Hz, CH_2CH_3), 1.41 (3H, d, J = 6.0 Hz, CH_3CH), 1.15 (3H, t, J = 7.0 Hz, CH_3CH_2); δC (75MHz, $CDCl_3$) 174.4, 154.0, 69.5, 50.8, 29.6, 19.7, 8.7; IR (Film / cm^{-1}) 1775 ($C=O_{ox}$), 1702 (C=O); LRMS : m/z (CI) 175.1 (100%) $[M+NH_4]^+$, 158.0 (20%) $[M+H]^+$; HRMS : m/z (ES) $[M+H]^+$ requires 158.0812, found 158.0812.

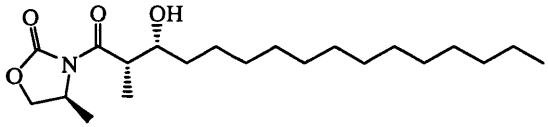
3.2.3 Tetradecanal 122



DMSO (2 equivalents) was added dropwise to a solution of oxalyl chloride (1.17 equivalents) in dry dichloromethane (10 cm^3) under nitrogen at -40°C and stirred for 5 minutes. Tetradecanol (1 equivalent) was then added as a solution in dry dichloromethane and stirred for 5 minutes. Triethylamine (4 equivalents) was then

added dropwise, the solution was allowed to warm to room temperature and stirred for an additional hour. The reaction was quenched with distilled water (5 cm^3), extracted with dichloromethane (3 x 10 cm^3), washed with saturated aqueous hydrogen carbonate solution (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **122** as a clear oil 73% yield, which matched the previously published data for this compound;[187] R_f (CH_2Cl_2) = 0.89; δH (300 MHz, $CDCl_3$) 9.76 (1H, t, J = 2.0 Hz, CHO), 2.41 (2H, td, J = 7.0 Hz and 2.0 Hz, CHOCH_2), 1.35 (22H, m, $C_{11}H_{22}$), 0.88 (3H, t, J = 8.5 Hz, CH_3); δC (75MHz, $CDCl_3$) 203.4, 44.3, 32.3, 30.1, 30.0, 29.9, 29.8, 29.7, 29.6, 23.1, 22.5, 14.5; IR (Film / cm^{-1}) 1728 (C=O).

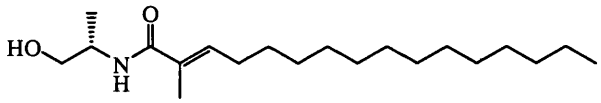
3.2.4 (*S*)-3-((2*S*,3*R*)-3-Hydroxy-2-methyl-hexadecanoyl)-4-methyl-oxazolidin-2-one 123



9BBN-OTf (1.1 equivalents, 0.5 mol dm^{-3} solution in hexane) was added dropwise to a stirred solution of (*S*)-4-methyl-3-propionyloxazolidin-2-one **121** (1 equivalent) in dry dichloromethane (10 cm^3) at 0°C, under nitrogen. After 30 minutes, diisopropylethylamine (1.2 equivalents) was added dropwise and the resulting solution stirred for a further 30 minutes. The solution was cooled to -78°C and tetradecanal **122** (1.1 equivalents) was added dropwise as a solution in dry dichloromethane. The reaction was allowed to warm to room temperature overnight. The reaction was quenched with Na_2PO_4/NaH_2PO_4 buffer solution (pH7, 10 cm^3), and stirred for 10 minutes before the addition of 2:1 methanol/hydrogen peroxide solution (30%, 10 cm^3), and stirred for a further 2 hours. The mixture was extracted with dichloromethane (3 × 20 cm^3), washed with aqueous saturated sodium hydrogen carbonate solution (10 cm^3), brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. The diastereomeric excess

was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. The relative and absolute stereochemistry was assumed as drawn from literature precedent and the small α-proton coupling constant (2.5 Hz). Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **123** as a yellow oil in 81% yield; R_f (CH_2Cl_2) = 0.63; $[\alpha]_D^{22}$ = +40 (c = 0.60, $CHCl_3$); δH (300 MHz, $CDCl_3$) 4.57 (1H, m, CHN), 4.42 (1H, app. t, J = 8.5 Hz, OCH_AH_B), 3.98 (1H, dd, J = 8.5 Hz and 3.0 Hz, OCH_AH_B), 3.90 (1H, m, CHOH), 3.72 (1H, qd, J = 7.0 Hz and 2.5 Hz, $CHCH_3$), 2.62 (1H, broad s, OH), 1.38 (3H, d, J = 6.5 Hz, CH_3CHN), 1.31-1.15 (26H, m, $C_{13}H_{26}$), 1.18 (3H, obs. d, J = 7.0 Hz, CH_3CH), 0.85 (3H, t, J = 7.0 Hz, alkyl-CH_3); δC (75MHz, $CDCl_3$) 176.5, 152.2, 70.7, 68.4, 49.8, 41.4, 33.2, 31.3, 29.1, 29.0, 28.8, 25.4, 22.1, 18.5, 13.5, 9.7; IR (Film / cm^{-1}) 3428 (broad O-H), 1781 ($C=O_{ox}$), 1704 (C=O); LRMS : m/z (CI) 387.4 (10%) $[M+NH_4]^+$, 370.3 (20%) $[M+H]^+$; HRMS : m/z (ES) $[M+H]^+$ requires 370.2952, found 370.2950.

3.2.5 (*E*)-*N*-((*R*)-1-Hydroxypropan-2-yl)-2-methylhexadec-2-enamide (*Semiplenamide C*) 119

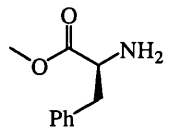


Potassium *tert*-butoxide (1.1 equivalents) was added in one portion to a solution of (*S*)-3-((2*S*,3*R*)-3-Hydroxy-2-methyl-hexadecanoyl)-4-methyl-oxazolidin-2-one **123** (1 equivalent) at -78°C in dry THF under nitrogen, and allowed to warm to room temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride solution (5 cm^3), extracted with ethyl acetate (3 x 20 cm^3), washed with saturated aqueous sodium hydrogen carbonate solution (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **119** as a clear oil in 85% yield, which matched the previously published data for this compound;[188] R_f (CH_2Cl_2) = 0.24; $[\alpha]_D^{25}$ = -8 (c = 0.61, $CHCl_3$); δH (300 MHz,

$CDCl_3$) 6.37 (1H, app. td, J = 7.5 Hz and 1.5 Hz, C*H*=C), 5.83 (1H, broad s, NH), 4.12 (1H, app. qd, J = 6.5 Hz and 3.5 Hz, C*H*CH_3), 3.71 (1H, dd, J = 11.0 Hz and 3.5 Hz, CH_AH_BOH), 3.56 (1H, dd, J = 11.0 Hz and 6.0 Hz, CH_AH_BOH), 2.13 (2H, app. q, J = 7.0 Hz, CH_2CH=C), 1.42 (1H, broad s, OH), 1.35-1.21 (22H, m, $C_{11}H_{22}$), 1.21 (3H, obs. d, J = 7.0 Hz, CH_3CH), 0.88 (3H, t, J = 7.0 Hz, alkyl-CH_3); δC (75MHz, $CDCl_3$) 169.3, 136.1, 129.2, 66.7, 47.1, 30.9, 29.3, 28.7, 28.6, 28.5, 28.4, 28.3, 27.8, 27.4, 21.7, 16.1, 13.1, 11.7; IR (KBr / cm^{-1}) 3280 (broad O-H), 1621 (C=O); LRMS : m/z (CI) 326.4 (100%) $[M+H]^+$; HRMS : m/z (ES) $[M+H]^+$ requires 326.3054, found 326.3052.

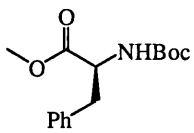
Chapter 3.3 General procedures for the synthesis of SuperQuat chiral auxiliary

3.3.1 (*S*)-Phenylalanine methyl ester 127



The preparation of the title compound was adapted from the previously published procedure.[189] Thionyl chloride (2 equivalents) was added dropwise to a solution of (*S*)-phenylalanine (1 equivalent) in methanol (2 cm^3 $mmol^{-1}$) at 0°C, under nitrogen. The reaction was allowed to warm to room temperature and stirred for 24 hours. The solvent was removed under reduced pressure to give the crude product, which matched the previously published data for this compound.[189] The crude product was carried on to the next step without further purification; δH (300 MHz, $CDCl_3$) 7.31-7.19 (5H, m, Ph), 3.75 (1H, dd, J = 8.0 Hz and 5.0 Hz, NH_2CH), 3.72 (3H, s, CH_3O), 3.07 (1H, dd, J = 13.5 Hz and 5.0 Hz, CH_AH_BPh), 2.87 (1H, dd, J = 13.5 Hz and 5.0 Hz, CH_AH_BPh).

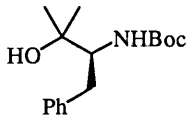
3.3.2 (*S*)-*N*-Boc-phenylalanine methyl ester 128



The preparation of the title compound was adapted from the previously published procedure.[189] Boc anhydride (1.1 equivalents) was added in one portion to a solution of (*S*)-phenylalanine methyl ester **127** in absolute ethanol (sufficient to dissolve the compound) at 0°C. Solid sodium hydrogen carbonate (2 equivalents) was added in one portion and the reaction was stirred for 48 hours. The solvent was then removed

under reduced pressure and the crude mixture dissolved in ether (50 cm^3). The mixture was filtered through a pad of Celite with ether as eluent (3 x 20 cm^3). The solvent was removed under reduced pressure to give the crude product **141**, which matched the previously published data for this compound.[190] The crude product was carried on to the next step without further purification; δH (300 MHz, $CDCl_3$) 7.33-7.09 (5H, m, Ph,), 4.97 (1H, broad d, J = 7.5 Hz, NH), 4.59 (1H, m, NHC*H*), 3.71 (3H, s, OCH_3), 3.16-2.99 (2H, m, CH_2Ph), 1.41 (9H, s, Boc)

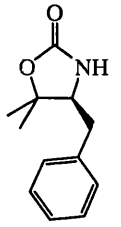
3.3.3 *tert*-Butyl-(*S*)-3-hydroxy-3-methyl-1-phenylbutan-2-ylcarbamate 129



The preparation of the title compound was adapted from the previously published procedure.[189] Methyl iodide (1 cm^3) was added dropwise with gentle heating to a suspension of magnesium turnings (4 equivalents) in dry THF (2 cm^3 $mmol^{-1}$) under nitrogen, until the reaction sustained a gentle reflux. Methyl iodide (4 equivalents, 1:5 solution in THF) was added dropwise over a period of thirty minutes. The solution was allowed to cool to room temperature, before (*S*)-*N*-Boc-phenylalanine methyl ester **128** (1 equivalent, 1:5 solution in THF) was added dropwise to the reaction over a period of thirty minutes. The reaction was stirred for 48 hours, quenched with saturated ammonium chloride solution (20 cm^3) and hydrochloric acid (20 cm^3, 1 mol dm^{-3} solution in water), filtered through Celite with ether as eluent (3 x 30 cm^3). The solvent was removed under reduced pressure, dissolved in ether (40 cm^3), washed with brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure give the crude product **129**, which was carried on to the next step without further purification; $[\alpha]_D^{25}$ = -45 (c = 1.00, $CHCl_3$); mp = 101-103°C; δH (300 MHz, $CDCl_3$) 7.24-7.09 (5H, m, Ph), 4.49 (1H, d, J = 9.0 Hz, NH), 3.62 (1H, m, C*H*NH), 3.02 (1H, dd, J = 14.0 Hz and 3.5 Hz, CH_AH_BPh), 2.53 (1H, m, CH_AH_BPh), 1.23 (6H, s, *gem*-dimethyl), 1.22 (9H, s, Boc); δC (75MHz, $CDCl_3$) 156.8, 139.4, 129.5, 128.7,

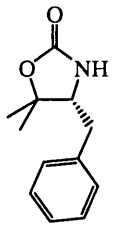
126.5, 79.7, 73.4, 60.8, 36.4, 28.6, 27.8, 26.9; IR (KBr / cm^{-1}) 3475 (O-H), 3379 (N-H), 1662 (C=O); HRMS : m/z (ES) $[M+H]^+$ requires 280.1907, found 280.1911.

3.3.4 (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one (SuperQuat) 126



The preparation of the title compound was adapted from the previously published procedure.[189] Potassium *tert*-butoxide (1.1 equivalents) was added in one portion to a solution of *tert*-butyl-(*S*)-3-hydroxy-3-methyl-1-phenylbutan-2-ylcarbamate **129** in dry THF (40 cm^3) under nitrogen, and stirred for thirty minutes at room temperature. The reaction was quenched with saturated ammonium chloride solution (10 cm^3), extracted with ether (3 x 20 cm^3), washed with saturated sodium hydrogen carbonate solution (10 cm^3), brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. Purification by recrystallisation (Et_2O, Hexane) gave **126** as a white solid in 77% yield, which matched the previously published data for this compound;[191] R_f (CH_2Cl_2) = 0.15; $[\alpha]_D^{25}$ = -120 (c = 0.78, $CHCl_3$); mp = 63-65°C; δH (300 MHz, $CDCl_3$) 7.34-7.08 (5H, m Ph), 5.09 (1H, broad s, NH), 3.63 (1H, dd, J = 10.5 Hz and 4.0 Hz, CHN), 2.77 (1H, dd, J = 13.5 Hz and 4.0 Hz, C$H_A$$H_B$Ph), 2.62 (1H, dd, J = 13.5 Hz and 10.0 Hz, C$H_A$$H_B$Ph), 1.39 (3H, s, (C$H_3$)C($CH_3$)), 1.38 (3H, s, ($CH_3$)C(C$H_3$)); δC (75MHz, $CDCl_3$) 158.3, 137.3, 129.5, 129.3, 127.6, 83.6, 63.5, 37.5, 27.9, 22.4.

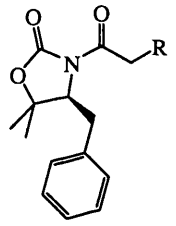
3.3.5 (*R*)-4-Benzyl-5,5-dimethyloxazolidin-2-one (SuperQuat) *ent*-126



The title compound was prepared as the same general procedure for **126** in 43% overall yield from the unnatural (*R*)-phenylalanine enantiomer, which matched the previously described data of the opposite enantiomer of this compound; $[\alpha]_D^{25}$ = +115 (c = 0.59, CH_2Cl_2).

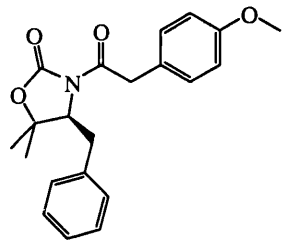
Chapter 3.4 General procedure for the preparation of *N*-acylated SuperQuat oxazolidin-2-ones using acid chlorides and bromides

3.4.1 General procedure



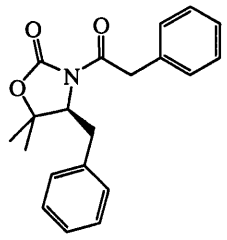
n-BuLi (1.01 equivalents, 2.5 mol dm^{-3} solution in hexane) was added to a solution of (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one (SuperQuat) **126** (1 equivalent) in dry THF (20 cm^3) at -78°C under nitrogen, and stirred for 30 minutes. The appropriate acid chloride or bromide (1.1 equivalents) was then added dropwise to the stirred solution over approximately 5 minutes and stirred for a further 2 hours, during which time the reaction was allowed to warm to 0°C. The reaction was quenched with aqueous saturated ammonium chloride solution (5 cm^3) and allowed to room temperature. The mixture was diluted with ethyl acetate (10 cm^3), washed with aqueous saturated sodium hydrogen carbonate solution, sufficient to dissolve the white precipitate, extracted with dichloromethane (3 x 20 cm^3), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product, which was purified either by silica gel chromatography or recrystallisation.

3.4.2 (*S*)-4-benzyl-3-(2-(4-methoxyphenyl)acetyl)-5,5-dimethyloxazolidin-2-one 165



The title compound was prepared as the general procedure from **126**, using 2-(4-methoxyphenyl)acetyl chloride. Purification by recrystallisation (Et_2O, Hexane) gave **165** as yellow solid in 80% yield; R_f (CH_2Cl_2) = 0.79; $[\alpha]_D^{25}$ = -30 (c = 0.77, CH_2Cl_2); mp = 67-69°C (Et_2O, Hexane); δH (300 MHz, $CDCl_3$) 7.31-7.20 (5H, m, Ph), 7.20 (2H, d, J = 9.0 Hz, *m*-MeOPh), 6.86 (2H, d, J = 9.0 Hz, *o*-MeOPh), 4.49 (1H, dd, J = 10.0 Hz and 4.0 Hz, CHN), 4.21 (2H, app. s, CH_2PhOMe), 3.81 (3H, s, CH_3O), 3.13 (1H, dd, J = 14.5 Hz and 4.0 Hz, PhCH_AH_B), 2.85 (1H, dd, J = 14.5 Hz and 10.0 Hz, PhCH_AH_B), 1.36 (3H, s, (CH_3)C(CH_3)), 1.31 (3H, s, (CH_3)C(CH_3)); δC (75MHz, $CDCl_3$) 172.2, 159.1, 153.0, 137.3, 131.1, 129.5, 129.0, 127.2, 126.1, 114.4, 82.7, 64.2, 55.7, 41.3, 35.6, 29.0, 22.7; IR (KBr / cm^{-1}) 1768 ($C=O_{ox}$), 1714 (C=O); LRMS : m/z (CI) 371.3 (70%) $[M+NH_4]^+$, 354.1 (90%) $[M+H]^+$; HRMS : m/z (ES) $[M+H]^+$ requires 354.1700, found 354.1703.

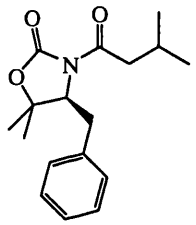
3.4.3 (*S*)-4-benzyl-5,5-dimethyl-3-(2-phenylacetyl)oxazolidin-2-one 164



The title compound was prepared as the general procedure from **126**, using phenylacetyl chloride. Purification by column chromatography (SiO_2, Et_2O:Hexane, 20:80) gave **143b** as clear oil in 73% yield; R_f (CH_2Cl_2) = 0.79; $[\alpha]_D^{25}$ = -16 (c =

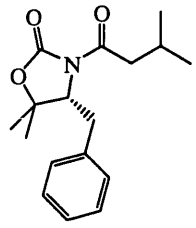
0.55, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.37-7.17 (10H, m, Ph), 4.50 (1H, dd, J = 10.0 Hz and 4.0 Hz, CHN), 4.28 (2H, app. s, $COCH_2$), 3.14 (1H, dd, J = 14.5 Hz and 10.0 Hz, CH_AH_BPh), 2.86 (1H, dd, J = 14.5 Hz and 4.0 Hz, CH_AH_BPh), 1.37 (3H, s, $(CH_3)C(CH_3)$, 1.32 (3H, s, $(CH_3)C(CH_3)$); δC (75MHz, $CDCl_3$) 171.9, 153.4, 137.2, 134.1, 130.1, 129.5, 129.1, 129.0, 127.6, 127.2, 82.8, 64.2, 42.2, 35.6, 29.0, 22.7; IR (Film / cm^{-1}) 1776 ($C=O_{ox}$), 1698 (C=O); LRMS : m/z (CI) 341.2 (100%) $[M+NH_4]^+$, 324.2 (70%) $[M+H]^+$; HRMS : m/z (ES) $[M+H]^+$ requires 324.1594, found 324.1594.

3.4.4 (*S*)-3-(3-methylbutanoyl)-4-benzyl-5,5-dimethyloxazolidin-2-one 181



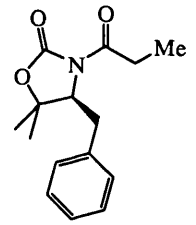
The title compound was prepared as the general procedure from **126**, using isovaleryl chloride. Purification *via* column chromatography (SiO_2; Et_2O:Hexane, 20:80) gave **181** as yellow oil in 76% yield; R_f (CH_2Cl_2) = 0.82; $[\alpha]_D^{25}$ = -34 (c = 0.59, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.31-7.17 (5H, m, Ph), 4.50 (1H, dd, J = 9.5 Hz and 4.0 Hz, CHN), 3.11 (1H, dd, J = 14.5 Hz and 4.0 Hz, $PhCH_AH_B$), 2.85 (1H, obs. dd, J = 14.5 Hz and 9.5 Hz, $PhCH_AH_B$), 2.78 (2H, app. d, J = 6.5 Hz, $COCH_2$), 2.13 (1H, m, isopropyl-CH), 1.34 (3H, s, $(CH_3)C(CH_3)$), 1.33 (3H, s, $(CH_3)C(CH_3)$), 0.94 (6H, app. d, J = 7.0 Hz, 2 x isopropyl-CH_3); δC (75MHz, $CDCl_3$) 173.3, 153.1, 137.4, 129.5, 129.1, 127.2, 82.5, 63.9, 44.6, 44.5, 35.8, 28.9, 25.6, 22.9, 22.7; IR (Film / cm^{-1}) 1779 ($C=O_{ox}$), 1700 (C=O); LRMS : m/z (CI) 307.2 (100%) $[M+NH_4]^+$, 290.1 (80%) $[M+H]^+$; HRMS : m/z (ES) $[M+H]^+$ requires 290.1751, found 290.1749.

3.4.5 (*R*)-3-(3-methylbutanoyl)-4-benzyl-5,5-dimethyloxazolidin-2-one *ent*-181



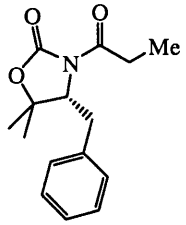
The title compound was prepared as the general procedure from *ent*-**126** using isovaleryl chloride. Purification by column chromatography (SiO_2; Et_2O:Hexane, 20:80) gave *ent*-**181** as yellow oil in 81%, which matched the previously described data for the opposite enantiomer of this compound; $[\alpha]_D^{25}$ = +41 (c = 1.16, CH_2Cl_2).

3.4.6 (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one 130



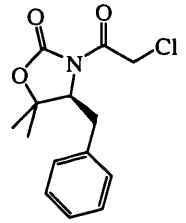
The title compound was prepared as the general procedure from **126**, using propionyl chloride. Purification by recrystallisation (Et_2O, Hexane) gave **130** as a white solid in 89% yield; R_f (CH_2Cl_2) = 0.79; $[\alpha]_D^{25}$ = -31 (c = 0.87, CH_2Cl_2); mp = 61-62°C (Et_2O, Hexane); δH (300 MHz, $CDCl_3$) 7.32-7.17 (5H, m, Ph), 4.49 (1H, dd, J = 9.5 Hz and 4.0 Hz, CHN), 3.12 (1H, dd, J = 14.5 Hz and 4.0 Hz, PhCH_AH_B), 2.89 (3H, obs. m, CH_2CH$_3$ and PhCH$_A$$H_B$), 1.35 (3H, s, (C$H_3$)C(CH$_3$)), 1.33 (3H, s, (CH$_3$)C(C$H_3$)), 1.17 (3H, t, J = 7.5 Hz, CH$_3$); δC (75MHz, $CDCl_3$) 174.7, 153.1, 137.4, 129.5, 129.1, 127.2, 82.6, 63.9, 35.8, 29.8, 29.0, 22.7, 8.8; IR (KBr / cm^{-1}) 1770 (C=O$_{ox}$), 1700 (C=O); LRMS : m/z (CI) 279.2 (100%) $[M+NH_4]^+$, 262.1 (50%) $[M+H]^+$; HRMS : m/z (ES) $[M+H]^+$ requires 262.1438, found 262.1442.

3.4.7 (*R*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one *ent*-130



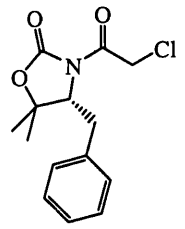
The title compound was prepared as the general procedure from *ent*-**126**, using propionyl chloride. Purification by recrystallisation (Et_2O, Hexane) gave *ent*-**130** as a white in 80%, which matched the previously described data for the opposite enantiomer of this compound; $[\alpha]_D^{25}$ = +28 (c = 0.99, CH_2Cl_2).

3.4.8 (*S*)-4-benzyl-3-(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one 166



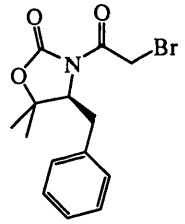
The title compound was prepared as the general procedure from **126**, using chloroacetyl chloride. Purification by recrystallisation (Et_2O, Hexane) gave **166** as a white solid in 81% yield; R_f (CH_2Cl_2) = 0.71; $[\alpha]_D^{25}$ = -39 (c = 1.00, $CHCl_3$); mp = 67-70°C (Et_2O, Hexane); δH (300 MHz, $CDCl_3$) 7.36-7.22 (5H, m, Ph), 4.80 (1H, d, J = 16.0 Hz, C*H*$_A$H$_B$Cl), 4.67 (1H, d, J = 16.0 Hz, CH$_A$*H*$_B$Cl), 4.52 (1H, dd, J = 10.0 Hz and 4.0 Hz, CHN), 3.22 (1H, dd, J = 14.5 Hz and 4.0 Hz, C*H*$_A$H$_B$Ph), 2.91 (1H, dd, J = 14.5 Hz and 10.0 Hz, CH$_A$*H*$_B$Ph), 1.41 (3H, s, (C*H*$_3$)C(CH$_3$)), 1.39 (3H, s, (CH$_3$)C(C*H*$_3$)); δC (75MHz, $CDCl_3$) 166.8, 152.7, 136.8, 129.4, 129.2, 127.4, 84.1, 64.5, 44.4, 35.4, 29.0, 22.8; IR (KBr / cm^{-1}) 1788 ($C{=}O_{ox}$), 1711 (C=O), 721 (C-Cl); LRMS : m/z (CI) 295.4 (20%) $[M+NH_4]^+$, 282.1 (30%) $[M+H]^+$; HRMS : m/z (ES) $[M+H]^+$ requires 282.0891, found 282.0888.

3.4.9 (*R*)-4-benzyl-3-(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one *ent*-166



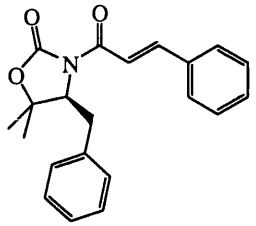
The title compound was prepared as the general procedure from *ent*-**126**, using chloroacetyl chloride. Purification by recrystallisation (Et_2O, Hexane) gave *ent*-**166** as a white solid in 79% yield, which matched the previously described data for the opposite enantiomer of this compound; $[\alpha]_D^{25}$ = +37 (c = 1.34, CH_2Cl_2).

3.4.10(*S*)-4-Benzyl-3-(2-bromoacetyl)-5,5-dimethyloxazolidin-2-one 167



The title compound was prepared as the general procedure from **126**, using bromoacetyl bromide. Purification by recrystallisation (Et_2O, Hexane) gave **167** as a yellow solid in 72% yield; R_f (CH_2Cl_2) = 0.74; $[\alpha]_D^{25}$ = -22 (c = 1.34, CH_2Cl_2); mp = 72-75°C (Et_2O, Hexane); δH (300 MHz, $CDCl_3$) 7.34-7.19 (5H, m, Ph), 4.56 (1H, d, J = 12.5 Hz, CH_AH$_B$Br), 4.49 (1H, dd, J = 10.0 Hz and 4.0 Hz, CHN), 4.42 (1H, d, J = 12.5 Hz, CH$_A$$H_B$Br), 3.18, (1H, dd, J = 14.5 Hz and 4.0 Hz, PhCH_AH$_B$), 2.89 (1H, dd, J = 14.5 Hz and 10.0 Hz, PhCH$_A$$H_B$), 1.38 (3H, s, (C$H_3$)C(CH$_3$)), 1.37 (3H, s, (CH$_3$)C(C$H_3$)); δC (75MHz, $CDCl_3$) 166.7, 152.5, 136.9, 129.4, 129.2, 127.4, 83.7, 63.4, 35.4, 29.0, 28.7, 22.7; IR (KBr / cm^{-1}) 1785 (C=O$_{ox}$), 1700 (C=O), 653 (C-Br); LRMS : m/z (CI) 344.1 (20%) $[M+NH_4]^+$; HRMS : m/z (ES) $[M+NH_4]^+$ requires 343.0652, found 343.0653.

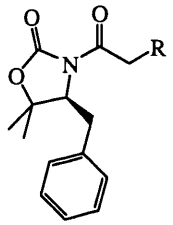
3.4.11 (*S*)-4-benzyl-5,5-dimethyl-3-((*E*)-3-phenylacryloyl)oxazolidin-2-one



The title compound was prepared as the general procedure from **126**, using cinnamoyl chloride. Purification by column chromatography (SiO_2, Et_2O:Hexane, 20:80) gave the tile compound as a yellow oil in 72% yield; R_f (CH_2Cl_2) = 0.74; $[\alpha]_D^{25}$ = -46 (c = 1.42, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.94 (1H, d, J = 16.0 Hz, PhCH=C*H*), 7.84 (1H, d, J = 16.0 Hz, PhC*H*=CH), 7.65-7.60 (2H, m, Ph), 7.43-7.21 (8H, m, Ph), 4.64 (1H, dd, J = 9.5 Hz and 3.5 Hz, CHN), 3.28 (1H, dd, J = 14.5 Hz and 3.5 Hz, C$H_A$$H_B$Ph), 2.94 (1H, dd, J = 14.5 Hz and 9.5 Hz, CH$_A$$H_B$Ph), 1.41 (3H, s, (C$H_3$)C($CH_3$), 1.40 (3H, s, ($CH_3$)C(C$H_3$); δC (75MHz, $CDCl_3$) 165.9, 153.2, 146.5, 137.5, 135.0, 131.0, 129.5, 129.3, 129.1, 129.0, 127.2, 117.8, 82.7, 64.3, 35.7, 29.0, 22.8 IR (Film / cm^{-1}) 1770 ($C=O_{ox}$), 1676 (C=O), 1620 (C=C); LRMS : m/z (CI) 355.3 (40%) $[M+NH_4]^+$, 336.2 (100%) $[M+H]^+$; HRMS : m/z (ES) $[M+H]^+$ requires 336.1594, found 336.1597.

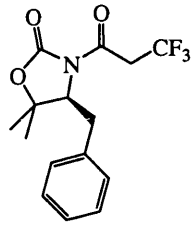
Chapter 3.5 General procedure for the preparation of *N*-acylated SuperQuat oxazolidin-2-ones using carboxylic acids

3.5.1 General procedure



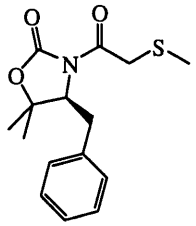
In a Schlenk flask, oxalyl chloride (1.2 equivalents) was added to a solution of the appropriate acid (1.1 equivalent) in dry THF at 0°C under nitrogen, and stirred for 5 minutes. DMF was then added (5 mol% with respect to oxalyl chloride) and the solution stirred at 0°C for 1 hour. The volatile material was then removed under reduced pressure and fresh dry THF (5 cm^3) was added. In a separate round-bottomed flask (100 cm^3), *n*-BuLi (1.01 equivalents, 2.5 mol dm^{-3} solution in hexane) was added dropwise to a solution of (S)-4-benzyl-5,5-dimethyl-oxazolidin-2-one **126** in dry THF at -78°C under nitrogen and stirred for 30 minutes. The newly formed acid chloride was then transferred from the Schlenk flask to the reaction *via* canella under nitrogen; additional dry THF (2 cm^3) was added to ensure complete transfer. The reaction was allowed to warm to 0°C over two hours before being quenched with saturated aqueous ammonium chloride solution (5 cm^3) and diluted with ethyl acetate (20 cm^3). The reaction was washed with saturated aqueous sodium hydrogen carbonate solution, sufficient to dissolve the white precipitate, extracted with dichloromethane (3 x 10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure giving the crude product, which was purified by silica gel chromatography.

3.5.2 (*S*)-3-(3,3,3,-Trifluoropropanoyl)-4-benzyl-5,5-dimethyloxazolidin-2-one 169



The title compound was prepared as the general procedure from **126** using trifluoropropanoic acid. Purification by column chromatography (SiO_2, CH_2Cl_2) gave **169** as a clear oil in 52% yield; R_f (CH_2Cl_2) = 0.78; $[\alpha]_D^{25}$ = -26 (c = 1.30, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.35-7.21 (5H, m, Ph), 4.54 (1H, dd, J = 9.5 Hz and 4.0 Hz, CHN), 3.95 (1H, dq, J = 16.0 Hz and 10.0 Hz, $CH_AH_BCF_3$), 3.80 (1H, dq, J = 16.0 Hz and 10.0 Hz, $CH_AH_BCF_3$), 3.18, (1H, dd, J = 14.0 Hz and 4.0 Hz, $PhCH_AH_B$), 2.91 (1H, dd, J = 14.0 Hz and 9.5 Hz, $PhCH_AH_B$), 1.41 (3H, s, $(CH_3)C(CH_3)$), 1.38 (3H, s, $(CH_3)C(CH_3)$); δC (75MHz, $CDCl_3$) 163.8, 152.7, 136.7, 129.4, 129.2, 127.5, 83.5, 64.1, 40.2 (q, J = 29.8 Hz), 35.5, 28.9, 22.6; IR (Film / cm^{-1}) 1778 ($C=O_{ox}$), 1713 (C=O), 1277 (C-F); LRMS : m/z (CI) 333.2 (100%) $[M+NH_4]^+$; HRMS : m/z (ES) $[M+NH_4]^+$ requires 333.1421, found 333.1423.

3.5.3 (*S*)-4-benzyl-5,5-dimethyl-3-(2-(methylthio)acetyl)oxazolidin-2-one 168

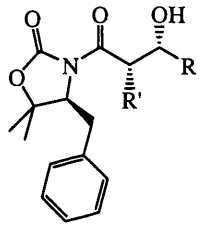


The title compound was prepared as the general procedure from **126** using 2-(methylthio)acetic acid. Purification by column chromatography (SiO_2, CH_2Cl_2) gave **168** as a yellow oil in 48% yield; R_f (CH_2Cl_2) = 0.68; $[\alpha]_D^{25}$ = +15 (c = 0.78, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.32-7.17 (5H, m, Ph), 4.49 (1H, dd, J = 9.5 Hz and

4.0 Hz, CHN), 3.76 (1H, d, J = 14.0 Hz, $CH_AH_BSCH_3$), 3.70 (1H, d, J = 14.0 Hz, $CH_AH_BSCH_3$), 3.12, (1H, dd, J = 14.0 Hz and 4.0 Hz, $PhCH_AH_B$), 2.89 (1H, dd, J = 14.0 Hz and 9.5 Hz, $PhCH_AH_B$), 2.11 (3H, s, SCH_3) 1.41 (6H, app. s, $(CH_3)C(CH_3)$), δC (75MHz, $CDCl_3$) 169.5, 152.8, 137.2, 129.7, 129.5, 129.1, 83.0, 64.0, 37.2, 35.8, 29.0, 22.7, 16.3; IR (Film / cm^{-1}) 1776 ($C=O_{ox}$), 1694 (C=O), 1358 (C-S); LRMS : m/z (CI) 311.2 (100%) $[M+NH_4]^+$, 294.2 (30%) $[M+H]^+$; HRMS : m/z (ES) $[M+NH_4]^+$ requires 311.1424, found 311.1427.

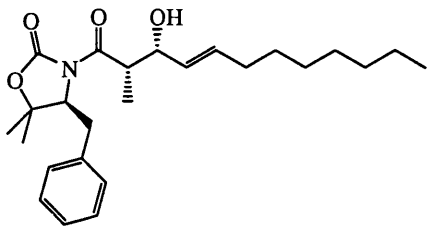
Chapter 3.6 General procedure for the *syn*-selective boron aldol reaction

3.6.1 General procedure



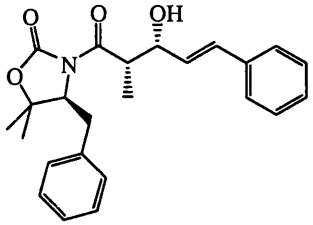
9BBN-OTf (1.1 equivalents, 0.5 mol dm^{-3} solution in hexane) was added dropwise to a stirred solution of the relevant acylated SuperQuat auxiliary (1 equivalent) in dry dichloromethane at 0°C, under nitrogen. After 30 minutes, diisopropylethylamine (1.2 equivalents) was added dropwise and the resulting solution stirred for a further 30 minutes. The solution was cooled to -78°C and the appropriate aldehyde (1.1 equivalents) was added dropwise, either neat or as a solution in dry dichloromethane. The reaction was then allowed to warm to room temperature overnight. The reaction was quenched with Na_2PO_4/NaH_2PO_4 buffer solution (pH7, 10 cm^3), and stirred for 10 minutes before the addition of 2:1 methanol-hydrogen peroxide solution (30%, 10 cm^3) and stirred for a further 2 hours. The mixture was extracted with dichloromethane (3 × 20 cm^3), washed with aqueous saturated sodium hydrogen carbonate solution (10 cm^3), brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product, which was purified either by silica gel chromatography or recrystallisation.

3.6.2 (*S*)-4-Benzyl-3-((*E*)-(2*S*,3*R*)-3-hydroxy-2-methyl-dodec-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 137b



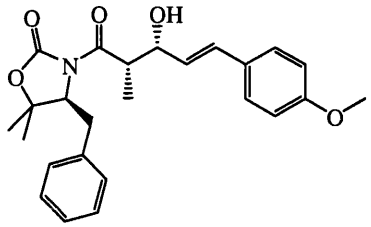
The title compound was prepared as the general procedure from (*E*)-dec-2-enal and (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **130**. The relative and absolute stereochemistry was assumed as drawn from literature precedent and the small α-proton coupling constant (4.0 Hz). The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **137b** as a yellow oil in 81% yield; R_f (CH_2Cl_2) = 0.32; $[\alpha]_D^{25}$ = -5 (c = 0.59, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.44-7.09 (5H, m, Ph), 5.67 (1H, dtd, J = 15.5 Hz, 7.0 Hz and 1.0 Hz, CH=C*H*C$_7$H$_{15}$), 5.39 (1H, ddt, 15.5, 6.0 and 1.0 Hz, C*H*=CHC$_7$H$_{15}$), 4.46 (1H, dd, J = 9.0 and 4.5 Hz, CHN), 4.30 (1H, m, C*H*OH), 3.83 (1H, qd, J = 7.0 Hz and 4.0 Hz, COCH), 2.99 (1H, dd, J = 14.0 and 4.5 Hz, CH_AH$_B$Ph), 2.83 (1H, dd, J = 14.0 and 9.0 Hz, CH$_A$CH_BPh), 2.53 (1H, broad s, OH), 1.96 (2H, app. q, J = 7.0 Hz, CH=CHCH_2), 1.32 (3H, s, (CH_3)C(CH$_3$)), 1.30 (3H, s, (CH$_3$)C(CH_3)), 1.29-1.13 (10H, m, alkyl-C$_5$H$_{10}$), 1.07 (3H, d, J = 7.0 Hz, CH_3CH), 0.81 (3H, t, J = 7.0 Hz, alkyl-CH$_3$); δC (75MHz, $CDCl_3$) 177.1, 152.6, 137.7, 134.1, 129.3, 129.2, 129.1, 127.3, 82.7, 73.4, 63.8, 43.3, 35.9, 32.7, 32.2, 29.6, 29.5, 23.1, 14.5, 12.0; IR (film / cm^{-1}) 3517 (broad O-H), 1778 (C=O$_{ox}$), 1698 (C=O); LRMS : m/z (CI) 175.1 (100%) $[M+NH_4]^+$, 158.0 (20%) $[M+H]^+$; LRMS : m/z (CI) 433.4 (90%) $[M+NH_4]^+$, 416.3 (100%) $[M+H]^+$; HRMS : no molecular ion found.

3.6.3 (*S*)-4-Benzyl-3-((*E*)-(2*S*,3*R*)-3-hydroxy-2-methyl-5-phenyl-pent-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 137a



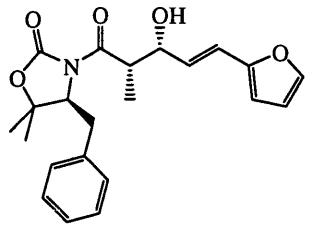
The title compound was prepared as the general procedure from (*E*)-cinnamaldehyde and (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **130**. The relative and absolute stereochemistry was assumed as drawn from literature precedent and the small α-proton coupling constant (4.0 Hz). The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **137a** as a white solid in 80% yield; m.p. 148-150°C (Et_2O); R_f (CH_2Cl_2) = 0.21; $[\alpha]_D^{25}$ = +4 (c = 1.07, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.36-7.13 (10H, m, Ph), 6.59 (1H, dd, J = 16.0 and 1.5 Hz, CH=C*H*Ph), 6.12 (1H, dd, J = 16.0 Hz and 6.0 Hz, C*H*=CHPh), 4.54 (1H, m, C*H*OH), 4.47 (1H, dd, J = 9.0 and 5.0 Hz, CHN), 3.94 (1H, qd, J = 7.0 and 4.0 Hz, COCH), 3.00 (1H, dd J = 14.0 and 5.0 Hz, CH_AH$_B$Ph), 2.84 (1H, dd, J = 14.0 and 9.0 Hz, CH$_A$CH_BPh), 2.74 (1H, broad s, OH), 1.32 (3H, s, (CH_3)C(CH$_3$)), 1.30 (3H, s, (CH$_3$)C(CH_3)), 1.13 (3H, d, J = 7.0 Hz, CH_3CH); δC (75MHz, $CDCl_3$) 177.1, 152.6, 137.7, 134.1, 129.3, 129.2, 129.1, 127.3, 82.7, 73.4, 63.8, 43.3, 35.9, 32.7, 32.2, 29.6, 29.5, 23.1, 14.5, 12.0; IR (KBr / cm^{-1}) 3517 (broad O-H), 1778 (C=O$_{ox}$), 1698 (C=O); LRMS : m/z (CI) 411.4 (100%) $[M+NH_4]^+$; HRMS : m/z (ES) $[M+NH_4]^+$ requires 411.2278, found 411.2273.

3.6.4 (*S*)-4-Benzyl-3-[(*E*)-(2*S*,3*R*)-3-hydroxy-5-(4-methoxy-phenyl)-2-methyl-pent-4-enoyl]-5,5-dimethyl-oxazolidin-2-one 137c



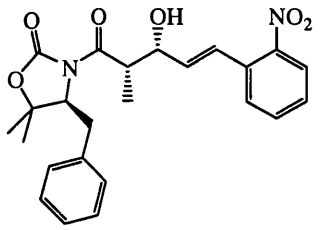
The title compound was prepared as the general procedure from *para*-methoxycinnamaldehyde and (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **130**. The relative and absolute stereochemistry was assumed as drawn from literature precedent and from the small α-proton coupling constant (4.0 Hz). The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **137c** as an yellow oil in 77% yield; R_f (CH_2Cl_2) = 0.17; $[\alpha]_D^{25}$ = +125 (c = 0.73, CH_3OH); δH (300 MHz, $CDCl_3$) 7.34-7.23 (7H, m, Ph), 6.84 (2H, d, J = 8.5 Hz, $MeOCH_AC\mathit{H}_BC$), 6.51 (1H, d, J = 16.0 Hz, CH=C*H*PhOMe), 5.99 (1H, dd, 16.0 Hz and 6.0 Hz, C*H*=CHPhOMe), 4.52-4.44 (2H, obs. m, C*H*OH and C*H*N), 3.97 (1H, qd, J = 7.0 and 4.0 Hz, $CH_3C\mathit{H}$), 3.73 (3H, s, CH_3O), 3.00 (1H, dd J = 14.5 and 4.5 Hz, $C\mathit{H}_AH_BPh$), 2.84 (1H, dd, J = 14.5 and 9.0 Hz, $CH_AC\mathit{H}_BPh$), 2.65 (1H, d, J = 3.0 Hz, OH), 1.31 (3H, s, $(C\mathit{H}_3)C(CH_3)$), 1.23 (3H, s, $(CH_3)C(C\mathit{H}_3)$), 1.13 (3H, d, J = 7.0 Hz, $C\mathit{H}_3CH$); δC (75MHz, $CDCl_3$) 176.1, 159.7, 152.8, 137.0, 131.7, 129.7, 129.5, 129.1, 128.2 127.8, 126.7, 114.4 82.7, 73.6, 63.7, 55.7, 43.4, 35.9, 28.7, 22.6, 12.2; IR (film / cm^{-1}) 3475 (broad O-H), 1773 ($C=O_{ox}$), 1700 (C=O), 1512 (MeO); LRMS : m/z (CI) 441.2 (50%) $[M+NH_4]^+$; HRMS : m/z (ES) $[M+NH_4]^+$ requires 441.2384, found 441.2382.

3.6.5 (*S*)-4-Benzyl-3-((*E*)-(2*S*,3*R*)-5-furan-2-yl-3-hydroxy-2-methyl-pent-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 137e



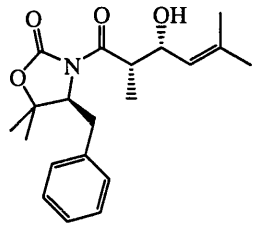
The title compound was prepared as the general procedure from (*E*)-3-(furan-2-yl)acrylaldehyde and (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **130**. The relative and absolute stereochemistry was assumed as drawn from literature precedent and from the small α-proton coupling constant (4.0 Hz). The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **137e** as a white solid in 85% yield; mp = 135-137°C (Et_2O, Hexane); R_f (CH_2Cl_2) = 0.15; $[\alpha]_D^{25}$ = +122 (c = 0.93, CH_3OH); δH (300 MHz, $CDCl_3$) 7.27-7.12 (6H, obs. m, Ph and Furyl-OCH), 6.42 (1H, dd, J = 16.0 Hz and 1.5 Hz, Furan-C*H*=CH), 6.28 (1H, dd, J = 3.0 Hz and 2.0 Hz, Furyl-OCH=C*H*), 6.15 (1H, d, 3.0 Hz, Furyl-CH), 6.04 (1H, dd, J = 16.0 Hz and 5.5 Hz, Furan-CH=C*H*), 4.59-4.45 (2H, obs. m and dd, J = 9.0 Hz and 5.0 Hz, C*H*OH and C*H*N), 3.90 (1H, qd, J = 7.0 Hz and 4.0 Hz, CH_3CH), 2.99 (1H, dd, J = 14.5 Hz and 5.0 Hz, CH_AH_BPh), 2.84 (1H, dd, J = 14.5 Hz and 9.0 Hz, CH_ACH_BPh), 2.75 (1H, d, J = 3.0 Hz, OH), 1.32 (3H, s, (CH_3)C(CH_3)), 1.26 (3H, s, (CH_3)C(CH_3)), 1.12 (3H, d, J = 7.0 Hz, CH_3CH); δC (75MHz, $CDCl_3$) 177.6, 152.8, 152.7, 142.4, 137.0, 129.5, 129.1, 127.6, 127.3 120.2, 111.7, 108.7, 82.8, 72.7, 63.7, 43.8, 35.7, 28.5, 22.6, 12.0; IR (KBr / cm^{-1}) 3444 (broad O-H), 1770 ($C=O_{ox}$), 1686 (C=O); LRMS : m/z (CI) 401.2 (40%) $[M+NH_4]^+$; HRMS : m/z (ES) $[M+NH_4]^+$ requires 401.2071, found 401.2069.

3.6.6 (*S*)-4-Benzyl-3-[(*E*)-(2*S*,3*R*)-3-hydroxy-2-methyl-5-(2-nitro-phenyl)-pent-4-enoyl]-5,5-dimethyl-oxazolidin-2-one 137d



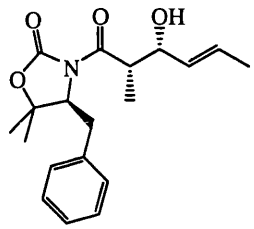
The title compound was prepared as the general procedure from *ortho*-nitrocinnamaldehyde and (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **130**. The relative and absolute stereochemistry was assumed as drawn from literature precedent and from the small α-proton coupling constant (4.0 Hz). The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **137d** as clear oil in 87% yield; R_f (CH_2Cl_2) = 0.12; $[\alpha]_D^{25}$ = -8 (c = 0.79, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.92 (1H, d, J = 8.0 Hz, *o*-C*H*PhNO$_2$), 7.61-7.19 (8H, m, Ph and Ph-NO$_2$), 7.12 (1H, dd, J = 16.0 Hz and 1.5 Hz, NO$_2$-PhC*H*=CH), 6.17 (1H, dd, J = 16.0 Hz and 5.5 Hz, NO$_2$-PhCH=C*H*), 4.67 (1H, m, C*H*OH), 4.59 (1H, dd, J = 9.0 Hz and 5.0 Hz, CHN), 4.06 (1H, qd, J = 7.0 and 4.0 Hz, CH$_3$C*H*), 3.08 (1H, dd J = 14.0 Hz and 5.0 Hz, CH_AH$_B$Ph), 2.90-2.80 (2H, obs. m, CH$_A$CH_BPh and OH), 1.40 (3H, s, (C*H*$_3$)C(CH$_3$)), 1.37 (3H, s, (CH$_3$)C(C*H*$_3$)), 1.21 (3H, d, J = 7.0 Hz, C*H*$_3$CH); δC (75MHz, $CDCl_3$) 176.6, 153.0, 146.2, 136.9, 134.9, 133.6, 133.0, 129.5, 129.3, 129.1, 128.6, 127.4, 128.3 124.9, 82.9, 72.9, 63.7, 43.1, 35.7, 28.8, 22.6, 12.0; IR (film / cm^{-1}) 3447 (broad OH), 1773 (C=O$_{ox}$), 1700 (C=O), 1552 (NO$_2$), 1352 (NO$_2$); LRMS : m/z (CI) 456.2 (100%) [M+NH$_4$]$^+$; HRMS : m/z (ES) [M+NH$_4$]$^+$ requires 456.2129, found 456.2123.

3.6.7 (*S*)-4-Benzyl-3-((2*S*,3R)-3-hydroxy-2,5-dimethyl-hex-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 137h



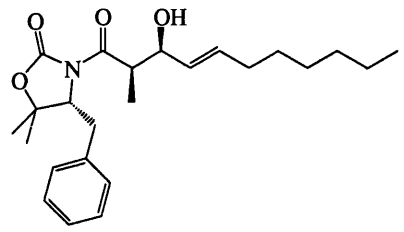
The title compound was prepared as the general procedure from 3-methylcrotonaldehyde and (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **130**. The relative and absolute stereochemistry was assumed as drawn from literature precedent and from the small α-proton coupling constant (5.0 Hz). The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **137h** as a yellow oil in 76% yield; R_f (CH_2Cl_2) = 0.18; $[\alpha]_D^{25}$ = -15 (c = 2.44, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.35-7.17 (5H, m, Ph), 5.23 (1H, d, J = 9.0 Hz, C=CH), 4.60 (1H, m, C*H*OH), 4.52 (1H, dd, J = 9.0 Hz and 4.5 Hz, CHN), 3.93 (1H, qd, J = 7.0 and 5.0 Hz, CH_3CH), 3.05 (1H, dd J = 14.5 Hz and 4.5 Hz, CH_AH_BPh), 2.90 (1H, dd, J = 14.5 Hz and 9.0 Hz, CH_ACH_BPh), 2.35 (1H, broad s, OH), 1.72 (3H, s (CH_3)(CH_3)C=CH), 1.68 (3H, s (CH_3)(CH_3)C=CH), 1.39 (3H, s, (CH_3)C(CH_3)), 1.37 (3H, s, (CH_3)C(CH_3)), 1.18 (3H, d, J = 7.0 Hz, CH_3CH); δC (75MHz, $CDCl_3$) 176.7, 153.0, 137.2, 137.1, 129.5, 129.1, 127.3, 124.5, 82.6, 69.9, 63.8, 43.4, 35.9, 28.6, 26.4, 22.5, 18.8, 12.6; IR (film / cm^{-1}) 3485 (broad O-H), 1778 ($C=O_{ox}$), 1695 (C=O); LRMS : m/z (CI) 175.1 (100%) $[M+NH_4]^+$, 158.0 (20%) $[M+H]^+$; HRMS: m/z (ES) $[M+H]^+$ requires 346.2013, found 346.2011.

3.6.8 (*S*)-4-Benzyl-3-((*E*)-(2*S*,3*R*)-3-hydroxy-2-methyl-hex-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 137g



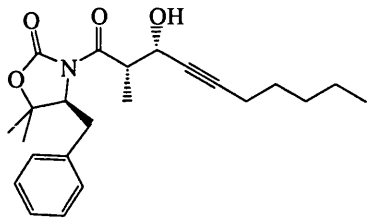
The title compound was prepared as the general procedure from (*E*)-crotonaldehyde and (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **130**. The relative and absolute stereochemistry was assumed as drawn from literature precedent and from the small α-proton coupling constant (4.5 Hz). The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* recrystallisation of the crude reaction mixture (Et_2O, Hexane) gave **137g** as a white solid in 76% yield; R_f (CH_2Cl_2) = 0.20; $[\alpha]_D^{25}$ = -14 (c = 0.84, CH_2Cl_2); mp = 81-84°C (Et_2O, Hexane); δH (300 MHz, $CDCl_3$) 7.39-7.17 (5H, m, Ph), 5.74 (1H, dqd, J = 15.5 Hz, 6.5 Hz and 1.0 Hz, CH=C*H*CH_3), 5.48 (1H, ddd, J = 15.5 Hz, 6.5 Hz and 1.5 Hz, C*H*=$CHCH_3$) 4.60 (1H, dd, J = 9.0 Hz and 4.5 Hz, CHN), 4.53 (1H, m, C*H*OH), 3.91 (1H, qd, J = 7.0 and 4.5 Hz, CH_3CH), 3.05 (1H, dd J = 14.5 Hz and 4.5 Hz, CH_AH_BPh), 2.90 (1H, dd, J = 14.5 Hz and 9.0 Hz, CH_ACH_BPh), 2.60 (1H, d, J = 2.5 Hz, OH), 1.70 (3H, d, J = 6.5 Hz, CH_3CH=CH), 1.39 (3H, s, (CH_3)C(CH_3)), 1.38 (3H, s, (CH_3)C(CH_3)), 1.15 (3H, d, J = 7.0 Hz, CH_3CH); δC (75MHz, $CDCl_3$) 176.9, 152.9, 137.1, 130.6, 129.5, 129.1, 128.9, 127.3, 82.7, 73.6, 63.8, 43.2, 35.9, 28.7, 22.5, 18.2, 12.1; IR (KBr / cm^{-1}) 3508 (broad O-H), 1775 ($C=O_{ox}$), 1696 (C=O); LRMS : m/z (CI) 349.3 (90%) $[M+NH_4]^+$, 332.3 (100%) $[M+H]^+$; HRMS: m/z (ES) $[M+H]^+$ requires 332.1856, found 332.1855.

3.6.9 (*R*)-4-Benzyl-3-((*E*)-(2*R*,3*S*)-3-hydroxy-2-methyl-undec-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 180a



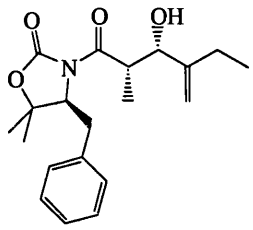
The title compound was prepared as the general procedure from (*E*)-non-2-enal and (*R*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one *ent*-**130**. The relative and absolute stereochemistry was assumed as drawn from literature precedent and from the small α-proton coupling constant (4.0 Hz). The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **180a** as a yellow oil in 81% yield; R_f (CH_2Cl_2) = 0.32; $[\alpha]_D^{25}$ = +8 (c = 1.36, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.35-7.19 (5H, m, Ph), 5.73 (1H, dtd, J = 14.5, 7.0 and 1.0 Hz, CH=C*H*C_6H_{13}), 5.44 (1H, ddt, J = 15.5, 6.5 and 1.5 Hz, C*H*=CHC_6H_{13}), 4.53 (1H, dd, J = 9.0 and 5.0 Hz, CHN), 4.37 (1H, m, C*H*OH), 3.89 (1H, qd, J = 7.0 and 4.0 Hz, COCH), 3.06 (1H, dd, J = 14.5 and 5.0 Hz, C$H_A$$H_B$Ph), 2.83 (1H, dd, J = 14.5 and 9.0 Hz, CH_ACH_BPh), 2.61 (1H, broad s, OH), 2.07-1.97 (2H, app. q, J = 7.0 Hz, CH=CHCH_2), 1.39 (3H, s, (CH_3)C(CH_3)), 1.38 (3H, s, (CH_3)C(CH_3)), 1.38-1.12 (8H, m, alkyl-C_4H_8), 1.15 (3H, d, J = 7.0 Hz, CH_3CH), 0.88 (3H, t, J = 7.0 Hz, alkyl-CH_3); δC (75MHz, $CDCl_3$) 177.0, 152.5, 136.7, 133.7, 129.1, 128.7, 127.0, 82.3, 73.0, 63.4, 43.0, 35.4, 32.3, 31.8, 29.2, 28.8, 27.3, 22.6, 22.5, 22.1, 14.1, 11.7; IR (film / cm^{-1}) 3509 (broad O-H), 1777 (C=O_{ox}), 1699 (C=O); LRMS : m/z (ES) 424.2 (100%) $[M+Na]^+$; HRMS : no molecular ion found.

3.6.10(*S*)-4-Benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-dec-4-ynoyl)-5,5-dimethyl-oxazolidin-2-one 138



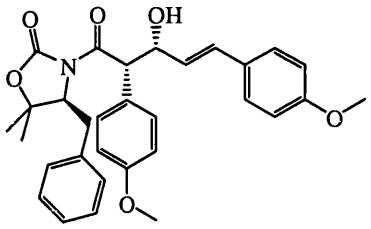
The title compound was prepared as the general procedure using oct-2-ynal and (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **130.** The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. The relative and absolute stereochemistry was assumed as drawn from literature precedent and from the small α-proton coupling constant (4.5 Hz). Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **138** as a yellow oil in 83% yield; R_f (CH_2Cl_2) = 0.48; $[\alpha]_D^{25}$ = -7 (c = 0.75, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.27-7.12 (5H, m, Ph), 4.60 (1H, m, C*H*OH), 4.47 (1H, dd, J = 9.0 Hz and 4.5 Hz, CHN), 3.85 (1H, qd, J = 7.0 and 4.5 Hz, CH_3CH), 2.99 (1H, dd J = 14.0 Hz and 4.5 Hz, CH_AH_BPh), 2.84 (1H, dd, J = 14.0 Hz and 9.0 Hz, CH_ACH_BPh), 2.60 (1H, d, J = 4.0 Hz, OH), 2.12 (2H, app. td, J = 7.0 Hz and 2.5 Hz, CCH_2), 1.48-1.19 (6H, m, alkyl-C_3H_6), 1.33 (3H, s, (CH_3)C(CH_3)), 1.31 (3H, s, (CH_3)C(CH_3)), 1.25 (3H, d, J = 7.0 Hz, CH_3CH), 0.82 (3H, t, J = 7.0 Hz, alkyl-CH_3); δC (75MHz, $CDCl_3$) 176.2, 152.6, 137.0, 129.6, 129.0, 127.3, 87.0, 82.8, 78.9, 64.0, 63.8, 44.6, 36.0, 31.4, 26.8, 26.5, 22.6, 19.1, 14.3, 12.9; IR (film / cm^{-1}) 3494 (broad O-H), 1778 ($C=O_{ox}$), 1698 (C=O); LRMS : m/z (CI) 403.4 (80%) $[M+NH_4]^+$, 386.4 (100%) $[M+H]^+$; HRMS : m/z (ES) $[M+H]^+$ requires 386.2326, found 386.2330.

3.6.11(*S*)-4-Benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylene-hexanoyl)-5,5-dimethyl-oxazolidin-2-one 256



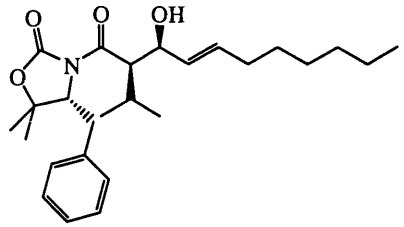
The title compound was prepared as the general procedure from 2-ethylacrolein and (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **130**. The relative and absolute stereochemistry was assumed as drawn from literature precedent and from the small α-proton coupling constant (4.0 Hz). The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* recrystallisation (Et_2O, Hexane) gave **256** as a white solid in 81% yield; R_f (CH_2Cl_2) = 0.28; $[\alpha]_D^{25}$ = -36 (c = 1.00, $CHCl_3$); mp (Et_2O, Hexane) = 52-53°C; δH (300 MHz, $CDCl_3$); 7.34-7.20 (5H, m, Ph), 5.16 (1H, app. t, J = 1.1 Hz, C*H*$_{cis}$H$_{trans}$=C), 4.98 (1H, app. t, J = 1.1 Hz, CH$_{cis}$*H*$_{trans}$=C), 4.53 (1H, dd, J = 9.0 Hz and 4.5 Hz, CHN), 4.40 (1H, m, C*H*OH), 3.96 (1H, qd, J = 7.0 Hz and 4.0 Hz, C*H*CH$_3$), 3.08 (1H, dd, J = 14.5 Hz and 4.5 Hz, C*H*$_A$H$_B$Ph), 2.91 (1H, dd, J =14.5 Hz and 9.0 Hz, CH$_A$*H*$_B$Ph), 2.79 (1H, broad s, OH), 2.02 (2H, m, C*H*$_2$CH$_3$), 1.40 (3H, s, (C*H*$_3$)C(CH$_3$)), 1.38 (3H, s, (CH$_3$)C(C*H*$_3$)), 1.11 (3H, d, J = 7.0 Hz, C*H*$_3$CH), 1.07 (3H, t, J = 7.5 Hz, C*H*$_3$CH$_2$); δC (75MHz, $CDCl_3$) 177.2, 152.2, 149.7, 136.5, 129.1, 128.7, 126.9, 100.5, 82.4, 73.6, 63.4, 40.6, 35.4, 28.4, 25.3, 22.8, 12.1, 10.6; IR (KBr / cm^{-1}) 3529 (broad O-H), 1774 (C=O$_{ox}$), 1683 (C=O); LRMS : m/z (CI) 363.3 (10%) $[M+NH_4]^+$, 346.3 (40%) $[M+H]^+$; HRMS : m/z (ES) $[M+H]^+$ requires 386.2326, found 386.2330.

3.6.12(*S*)-4-Benzyl-3-[(*E*)-(2*S*,3*R*)-3-hydroxy-2,5-*bis*-(4-methoxy-phenyl)-pent-4-enoyl]-5,5-dimethyl-oxazolidin-2-one 165a



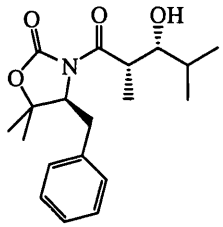
The title compound was prepared as the general procedure from *para*-methoxycinnamaldehyde and (*S*)-4-benzyl-3-(2-(4-methoxyphenyl)acetyl)-5,5-dimethyloxazolidin-2-one **165**. The relative and absolute stereochemistry of the major diastereomer was assumed as drawn from literature precedent. The diastereomeric excess was determined as 76% de by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **165a** as a yellow oil in 73% yield and 76% de; R_f (CH_2Cl_2) = 0.08; $[\alpha]_D^{25}$ = -52 (c = 1.07, CH_2Cl_2) at 76% de; δH (300 MHz, $CDCl_3$) 7.32 (2H, d, J = 8.5 Hz, *m*-PhOMe), 7.21 (2H, d, J = 8.5 Hz, *m*-PhOMe), 7.15-7.02 (5H, m, Ph), 6.82 (2H, d, J = 8.5 Hz, *o*-PhOMe), 6.75 (2H, d, J = 8.5 Hz, *o*-PhOMe), 5.52 (1H, d, J = 16.0 Hz, CH=C*H*PhOMe), 5.99 (1H, dd, J = 16.0 Hz and 7.0 Hz, C*H*=CHPhOMe), 5.11 (1H, m, C*H*PhOMe), 4.77 (1H, app. td, J = 7.5 Hz and 2.5 Hz, C*H*OH), 4.40 (1H, dd, J = 9.0 and 4.0 Hz, CHN), 3.74 (3H, s, PhOCH_3), 3.72 (3H, s, PhOCH_3) 2.84 (1H, dd, J = 14.5 Hz and 4.0 Hz, CH_AH$_B$Ph), 2.62 (1H, dd, J = 14.5 Hz and 9.0 Hz, CH$_A$CH_BPh), 2.26 (1H, broad s, OH), 1.19 (3H, s, (CH_3)C(CH$_3$)), 1.08 (3H, s, (CH$_3$)C(CH_3)); δC (75MHz, $CDCl_3$) 173.3, 159.8, 152.4, 137.0, 132.6, 131.4, 129.6, 129.4, 129.2, 129.0, 128.2, 127.1, 126.7, 126.4, 114.6, 114.3, 82.5, 74.7, 63.7, 55.7, 55.6, 54.9, 35.4, 28.5, 22.5; IR (film / cm^{-1}) 3502 (broad O-H), 1771 (C=O$_{ox}$), 1684 (C=O), 1250 (OMe); LRMS : m/z (CI) 533.3 (10%) $[M+NH_4]^+$; HRMS: m/z (ES) $[M+NH_4]^+$ requires 533.2646, found 533.2647.

3.6.13(*R*)-4-Benzyl-3-((*E*)-(2*R*,3*S*)-3-hydroxy-2-isopropyl-undec-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 182a



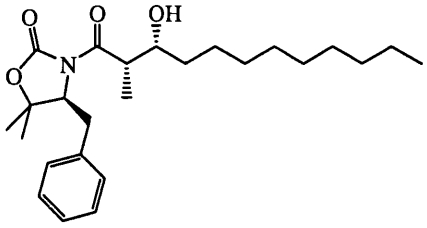
The title compound was prepared as the general procedure from (*E*)-non-2-enal and (*R*)-3-(3-methylbutanoyl)-4-benzyl-5,5-dimethyloxazolidin-2-one *ent*-**181**. The relative and absolute stereochemistry was assumed as drawn from literature precedent and from the small α-proton coupling constant (6.5 Hz). The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **182a** as a yellow oil in 81% yield; R_f (CH_2Cl_2) = 0.48; $[\alpha]_D^{25}$ = +22 (c = 0.85, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.27-7.11 (5H, m, Ph), 5.54-5.71 (2H, m, alkyl-C*H*=CH and alkyl-CH=C*H*), 4.53 (1H, dd, J = 10.0 Hz and 4.0 Hz, CHN), 4.36 (1H, app. t, J = 7.0 Hz, C*H*OH), 4.09 (1H, dd, J = 9.0 Hz and 6.5 Hz, isopropyl-CH), 3.09 (1H, dd, J = 14.5 Hz and 4.0 Hz, CH_AH$_B$Ph), 2.81 (1H, dd, J = 14.5 Hz and 10.0 Hz, CH$_A$$H_B$Ph), 2.04-1.88 (4H, obs. m, OH, CH=CHCH_2 and isopropyl-CH), 1.35-1.12 (8H, m, alkyl-C_4H_8), 1.24 (6H, app. s, $(CH_3)C(CH_3)$), 0.90 (3H, d, J = 7.0 Hz, isopropyl-CH_3), 0.82 (3H, obs. d, J = 7.0 Hz, isopropyl-CH_3), 0.80 (3H, obs. t, J = 7.0 Hz, alkyl-CH_3); δC (75MHz, $CDCl_3$) 174.7, 153.9, 137.4, 135.8, 129.5, 129.1, 128.9, 127.2, 82.4, 73.8, 64.3, 54.1, 35.9, 32.7, 32.1, 29.5, 29.3, 28.7, 28.6, 23.0, 22.6, 21.0, 20.4, 14.5; IR (film / cm^{-1}) 3501 (broad O-H), 1778 (C=O_{ox}), 1693 (C=O); LRMS : m/z (CI) 447.3 (80%) $[M+NH_4]^+$, 430.3 (100%) $[M+H]^+$; HRMS: m/z (ES) $[M+NH_4]^+$ requires 447.3217, found 447.3213.

3.6.14(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-hydroxy-2,4-dimethyl-pentanoyl)-5,5-dimethyl-oxazolidin-2-one 131



The title compound was prepared as the general procedure from isobutyraldehyde and (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **130**. The relative and absolute stereochemistry was assumed as drawn from literature precedent and from the small α-proton coupling constant (3.0 Hz). The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **131** as a clear oil in 82% yield; R_f (CH_2Cl_2) = 0.23; $[\alpha]_D^{25}$ = -32 (c = 0.56, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.34-7.20 (5H, m, Ph), 4.53 (1H, dd, J = 8.5 Hz and 4.5 Hz, CHN), 3.92 (1H, qd, J = 7.0 Hz and 3.0 Hz, COCH), 3.50 (1H, app. dt, J = 8.5 Hz, and 3.0 Hz, C*H*OH), 3.06 (1H, dd, J = 14.5 Hz and 4.5 Hz, CH_AH$_B$Ph), 2.91 (1H, dd, J = 14.5 Hz and 8.5 Hz, CH$_A$$H_B$Ph), 2.79 (1H, d, J = 3.0 Hz, OH), 1.70 (1H, m, isopropyl-CH), 1.40 (3H, s, (CH_3)C(CH$_3$)), 1.38 (3H, s, (CH$_3$)C(CH_3)), 1.16 (3H, d, J = 7.0 Hz, COCHCH_3), 1.01 (3H, d, J = 7.0 Hz, isopropyl-CH$_3$), 0.90 (3H, d, J = 7.0 Hz, isopropyl-CH$_3$); δC (75MHz, $CDCl_3$) 178.4, 156.2, 137.0, 129.5, 129.1, 127.3, 82.7, 77.0, 63.7, 40.2, 35.9, 31.1, 28.2, 22.6, 19.5, 19.3, 10.7; IR (Film / cm^{-1}) 3522 (broad OH), 1778 (C=O$_{ox}$), 1694 (C=O); LRMS : m/z (CI) 351.3 (10%) $[M+NH_4]^+$, 334.2 (80%) $[M+H]^+$; HRMS: m/z (ES) $[M+H]^+$ requires 334.2013, found 334.2014.

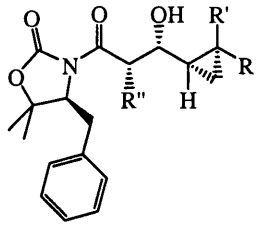
3.6.15(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-dodecanoyl)-5,5-dimethyl-oxazolidin-2-one 134



The title compound was prepared as the general procedure from decanal and (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **130**. The relative and absolute stereochemistry was assumed as drawn from literature precedent and from the small α-proton coupling constant (3.0 Hz). The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **134** as a yellow oil in 55% yield; R_f (CH_2Cl_2) = 0.41; $[\alpha]_D^{25}$ = -13 (c = 2.65, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.32-7.17 (5H, m, Ph), 4.52 (1H, dd, J = 9.0 Hz and 4.5 Hz, CHN), 3.87 (1H, m, C*H*OH), 3.73 (1H, qd, J = 7.0 Hz and 3.0 Hz, CH_3CH), 3.04 (1H, dd, J = 14.5 Hz and 4.5 Hz, CH_ACH_BPh), 2.88 (1H, dd, J = 14.5 Hz and 9.0 Hz, CH_AH_BPh), 2.75 (1H, broad s, OH), 1.64-1.18 (16H, m, alkyl-C_8H_{16}), 1.38 (3H, s, (CH_3)C(CH_3)), 1.36 (3H, s, (CH_3)C(CH_3)), 1.14 (3H, d, J = 7.0 Hz, CH_3CH), 0.85 (3H, t, J = 7.0 Hz, alkyl-CH_3); δC (75MHz, $CDCl_3$) 178.1, 152.7, 137.0, 129.5, 129.1, 127.3, 82.7, 72.0, 63.7, 42.6, 35.9, 34.1, 32.3, 30.0, 29.9, 29.7, 28.9, 26.4, 23.1, 22.6, 14.5, 11.0; IR (film / cm^{-1}) 3521 (broad O-H), 1779 ($C=O_{ox}$), 1683 (C=O); LRMS : m/z (CI) 418.3 (30%) $[M+H]^+$; HRMS: m/z (ES) $[M+H]^+$ requires 418.2952, found 418.2949.

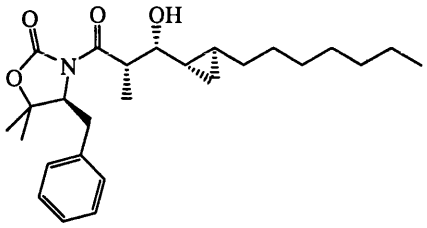
Chapter 3.7 General procedure for the hydroxyl-directed cyclopropanation of unsaturated *syn*-aldols

3.7.1 General procedure



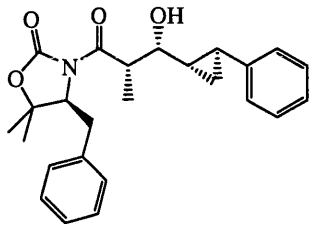
Diethyl zinc (5 equivalents, 1.0 mol dm^{-3} solution in hexane) was added in one portion *via* syringe to a stirred solution of *syn*-aldol (1 equivalent) in dry dichloromethane at -10°C, before the immediate addition of diiodomethane (5 equivalents) in one portion *via* syringe, under nitrogen and in the absence of light. The solution was allowed to warm to 0°C over 2 hours before being quenched with saturated sodium sulfite solution (5 cm^3) and stirred for 10 minutes. Hydrochloric acid (1.0 mol dm^{-3} solution in water) was then added, sufficient to dissolve the white precipitate. The crude product was extracted with dichloromethane (3 x 10 cm^3), washed with brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product, which was purified either by silica gel chromatography or recrystallisation. The all-*syn* stereochemistry was assigned as drawn due to literature precedent in the minimisation the $A^{1,3}$-strain in the transition state.

3.7.2 (*S*)-4-Benzyl-3-[(2*S*,3*R*)-3-((1*S*,2*S*)-2-heptyl-cyclopropyl)-3-hydroxy-2-methyl-propionyl]-5,5-dimethyl-oxazolidin-2-one 147b



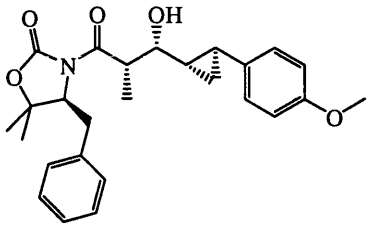
The title compound was prepared as the general procedure. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **147b** as a yellow oil in 89% yield; R_f (CH_2Cl_2) = 0.28; $[\alpha]_D^{25}$ = +9 (c = 0.59, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.30-7.12 (5H, m, Ph), 4.46 (1H, dd, J = 9.5 Hz and 4.5 Hz, CHN), 3.92 (1H, qd, J = 7.0 and 3.0 Hz, COCH), 3.15 (1H, dd, J = 8.5 Hz and 3.0 Hz, C*H*OH), 3.01 (1H, dd, J = 14.5 and 4.5 Hz, CH_AH$_B$Ph), 2.82 (1H, dd, J = 14.5 Hz and 9.5 Hz, CH$_A$CH_BPh), 2.50 (1H, broad s, OH), 1.31 (3H, s, (CH_3)C(CH$_3$)), 1.30 (3H, s, (CH$_3$)C(CH_3)), 1.26-1.14 (12H, obs. m, alkyl-C_6H_{12}), 1.18 (3H, d, J = 7.0 Hz, CH_3CH), 0.81 (3H, t, J = 7.0 Hz, alkyl-CH$_3$), 0.68 (1H, app. dtd, J = 12.5 Hz, 8.5 Hz and 4.0 Hz, (CH-cyclopropyl-C*H*), 0.60 (1H, m, alkyl-cyclopropyl-C*H*), 0.46 (1H, app. dt, J = 8.5 Hz and 4.5 Hz, cyclopropyl-CH_AH$_B$), 0.28 (1H, app. dt, J = 8.0 Hz and 5.0 Hz, cyclopropyl-CH$_A$$H_B$); δC (75MHz, $CDCl_3$) 177.3, 152.8, 137.1, 129.5, 129.1, 127.2, 82.6, 76.2, 63.9, 43.3, 35.8, 34.0, 32.3, 29.9, 29.8, 29.7, 28.9, 23.1, 22.6, 22.4, 17.0, 14.5, 11.6, 11.1; IR (film / cm^{-1}) 3515 (broad O-H), 1777 (C=O$_{ox}$), 1697 (C=O); LRMS : m/z (CI) 447.4 (70%) [M+NH$_4$]$^+$, 430.4 (100%) [M+H]$^+$; HRMS : m/z (ES) [M+H]$^+$ requires 430.4952, found 430.2955.

3.7.3 (*S*)-4-Benzyl-3-[(2*S*,3R)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-phenyl-cyclopropyl)-propionyl]-5,5-dimethyl-oxazolidin-2-one 147a



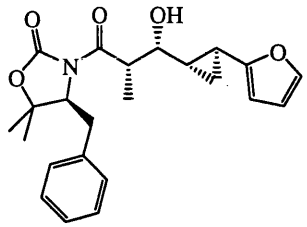
The title compound was prepared as the general procedure. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **147a** as a yellow oil in 95% yield; R_f (CH_2Cl_2) = 0.29; $[\alpha]_D^{25}$ = +58 (c = 2.30, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.28-6.93 (10H, m, Ph), 4.35 (1H, dd, J = 9.0 Hz and 5.0 Hz, CHN), 3.97 (1H, qd, J = 7.0 and 4.5 Hz, COCH), 3.37 (1H, m, C*H*OH), 3.00 (1H, dd, J = 14.5 Hz and 5.0 Hz, CH_AH$_B$Ph), 2.78 (1H, dd, J = 14.5 and 9.0 Hz, CH$_A$CH_BPh), 2.54 (1H, broad s, OH), 1.84 (1H, app. dt, J = 9.0 Hz and 5.0 Hz, Ph-cyclopropyl-C*H*), 1.25 (3H, s, (CH_3)C(CH$_3$)), 1.23 (1H, obs. m, CH-cyclopropyl-C*H*), 1.18 (3H, d, J = 7.0 Hz, CH_3CH), 1.04 (3H, s, (CH$_3$)C(CH_3)), 1.00 (1H, app. dt, J = 8.5 Hz and 5.5 Hz, cyclopropyl-CH_AH$_B$), 0.89 (1H, app. dt, J = 8.5 Hz and 5.5 Hz, cyclopropyl-CH$_A$$H_B$); δC (75MHz, $CDCl_3$) 176.8, 152.8, 142.7, 137.2, 129.5, 129.1, 128.8, 127.3, 126.2, 126.1, 82.6, 75.9, 63.8, 43.8, 35.7, 28.5, 27.0, 22.6, 21.7, 14.4, 12.9; IR (film / cm^{-1}) 3447 (broad O-H), 1772 (C=O$_{ox}$), 1685 (C=O); LRMS : m/z (CI) 425.3 (10%) [M+NH$_4$]$^+$; HRMS : m/z (ES) [M+NH$_4$]$^+$ requires 425.2435, found 425.2439.

3.7.4 (*S*)-4-Benzyl-3-{(2*S*,3*R*)-3-hydroxy-3-[(1*S*,2*S*)-2-(4-methoxy-phenyl)-cyclopropyl]-2-methyl-propionyl}-5,5-dimethyl-oxazolidin-2-one 147c



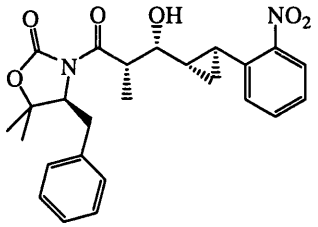
The title compound was prepared as the general procedure. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **147c** as a yellow oil in 90% yield; R_f (CH_2Cl_2) = 0.22; $[\alpha]_D^{25}$ = +58° (c = 0.86, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.34-7.28 (5H, m, Ph), 7.00 (2H, d, J = 8.5 Hz MeOCHC*H*C), 6.80 (2H, d, J = 8.5 Hz, MeOC*H*CHC), 4.39 (1H, dd, J = 9.0 Hz and 4.0 Hz, CHN), 3.91 (1H, qd, J = 7.0 and 4.5 Hz, COCH), 3.68 (3H, s, CH_3O), 3.36 (1H, m, C*H*OH), 3.01 (1H, dd, J = 14.5 Hz and 4.0 Hz, CH_AH$_B$Ph), 2.81 (1H, dd, J = 14.5 and 9.0 Hz, CH$_A$CH_BPh), 2.47 (1H, broad s, OH), 1.78 (1H, app. dt, J = 9.0 Hz and 5.5 Hz, MeOPh-cyclopropyl-C*H*), 1.28 (3H, s, (CH_3)C(CH$_3$)), 1.19 (1H, obs. m, CH-cyclopropyl-C*H*), 1.19 (3H, d, J = 7.0 Hz, CH_3CH), 1.12 (3H, s, (CH$_3$)C(CH_3)), 0.94 (1H, app. dt, J = 9.0 Hz and 5.0 Hz, cyclopropyl-CH_AH$_B$), 0.85 (1H, app. dt, J = 8.5 Hz and 5.0 Hz, cyclopropyl-CH$_A$$H_B$); δC (75MHz, $CDCl_3$) 177.0, 156.2, 152.8, 137.1, 134.5 129.5, 129.1, 127.3, 120.1, 114.4, 82.6, 75.9, 63.8, 55.7, 43.6, 35.7, 28.5, 26.3, 22.6, 20.6, 13.9, 12.5; IR (film / cm^{-1}) 3452 (broad O-H), 1772 (C=O$_{ox}$), 1700 (C=O), 1516 (MeO); LRMS : m/z (CI) 455.2 (40%) $[M+NH_4]^+$, 438.3 (40%) $[M+H]^+$; HRMS: m/z (ES) $[M+NH_4]^+$ requires 455.2540, found 455.2540.

3.7.5 (*S*)-4-Benzyl-3-[(2*S*,3*R*)-3-((1*S*,2*S*)-2-furan-2-yl-cyclopropyl)-3-hydroxy-2-methyl-propionyl]-5,5-dimethyl-oxazolidin-2-one 147e



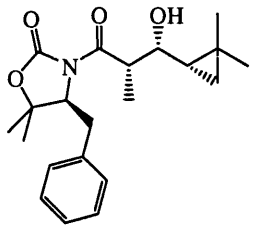
The title compound was prepared as the general procedure. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **147e** as a yellow oil in 92% yield; R_f (CH_2Cl_2) = 0.18; $[\alpha]_D^{25}$ = +56 (c = 1.00, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.29-7.12 (6H, m, Ph and furyl-OCH), 6.17 (1H, dd, J = 3.0 Hz and 2.0 Hz, furyl-OCHC*H*), 5.90 (1H, d, J = 3.0 Hz, furyl-CCH), 4.44 (1H, dd, J = 9.0 Hz and 4.5 Hz, CHN), 3.95 (1H, qd, J = 7.0 and 4.0 Hz, COCH), 3.43 (1H, m, C*H*OH), 3.01 (1H, dd, J = 14.5 Hz and 4.5 Hz, CH_AH$_B$Ph), 2.83 (1H, dd, J = 14.5 and 9.0 Hz, CH$_A$CH_BPh), 2.48 (1H, broad s, OH), 1.85 (1H, m, furan-cyclopropyl-CH), 1.36 (1H, obs. m, CH-cyclopropyl-C*H*), 1.31 (3H, s, (CH_3)C(CH$_3$)), 1.23 (3H, s, (CH$_3$)C(CH_3)), 1.21 (3H, d, J = 7.0 Hz, CH_3CH), 1.00-0.90 (2H, obs. m, cyclopropyl-CH_AH$_B$ and cyclopropyl-CH$_A$$H_B$); δC (75MHz, $CDCl_3$) 177.0, 156.1, 141.0, 137.1, 129.5, 129.1, 127.3, 110.7, 104.3, 82.7, 74.7, 63.8, 43.6, 35.8, 28.7, 23.9, 22.6, 22.6, 14.6, 12.4, 11.9; IR (film / cm^{-1}) 3502 (broad O-H), 1774 (C=O$_{ox}$), 1696 (C=O), 1516 (Furan-CO); LRMS : m/z (CI) 415.2 (100%) [M+NH$_4$]$^+$, 398.2 (80%) [M+H]$^+$; HRMS: m/z (ES) [M+NH$_4$]$^+$ requires 415.2227, found 415.2226.

3.7.6 (*S*)-4-Benzyl-3-{(2*S*,3*R*)-3-hydroxy-2-methyl-3-[(1*S*,2*S*)-2-(2-nitro-phenyl)-cyclopropyl]-propionyl}-5,5-dimethyl-oxazolidin-2-one 147d



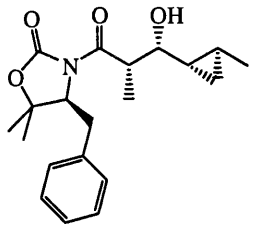
The title compound was prepared as the general procedure. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* recrystallisation (Et_2O) gave **147d** as a white solid in 91% yield; R_f (CH_2Cl_2) = 0.11; $[\alpha]_D^{25}$ = +57 (c = 0.86, CH_2Cl_2); mp = 101-104°C (Et_2O); δH (300 MHz, $CDCl_3$) 7.81 (1H, d, J = 8.0 Hz, NO_2C-*o*-CH), 7.49 (1H, app. td, J = 8.0 Hz and 1.5 Hz, NO_2C-*p*-CH), 7.35-7.19 (6H, obs. m, Ph and $NO_2CCHCCH$), 7.16 (1H, d, J = 8.0 Hz, NO_2CCCH), 4.53 (1H, dd, J = 9.5 Hz and 4.5 Hz, CHN), 4.04 (1H, qd, J = 7.0 Hz and 3.5 Hz, COCH), 3.75 (1H, m, C*H*OH), 3.07 (1H, dd, J = 14.5 Hz and 4.5 Hz, CH_AH_BPh), 2.90 (1H, dd, J = 14.5 and 9.5 Hz, CH_ACH_BPh), 2.43 (1H, d, J = 2.5 Hz, OH), 2.25 (1H, app. dt, J = 8.5 Hz and 5.5 Hz, NO_2Ph-cyclopropyl-C*H*), 1.38 (3H, s, (CH_3)C(CH_3)), 1.33 (3H, s, (CH_3)C(CH_3)), 1.28 (3H, d, J = 7.0 Hz, CH_3CH), 1.23 (2H, obs. m, cyclopropyl-CH_AH_B and CH-cyclopropyl-C*H*), 0.75 (1H, app. dt, J = 8.5 Hz and 5.5 Hz, cyclopropyl-CH_AH_B); δC (75MHz, $CDCl_3$) 177.2, 152.8, 151.1, 137.2, 137.0, 133.2, 129.5, 129.1, 128.2, 127.3, 127.0, 124.7, 82.7, 73.7, 63.7, 43.2, 35.9, 28.8, 25.5, 22.6, 17.4, 12.7, 12.3; IR (KBr / cm^{-1}) 3431 (broad O-H), 1769 ($C=O_{ox}$), 1684 (C=O), 1528 (NO_2), 1370 (NO_2); LRMS : m/z (CI) 470.2 (100%) $[M+NH_4]^+$, 453.2 (30%) $[M+H]^+$; HRMS: m/z (ES) $[M+NH_4]^+$ requires 470.2286, found 470.2287.

3.7.7 (*S*)-4-Benzyl-3-[(2*S*,3*R*)-3-((*S*)-2,2-dimethyl-cyclopropyl)-3-hydroxy-2-methyl-propionyl]-5,5-dimethyl-oxazolidin-2-one 147h



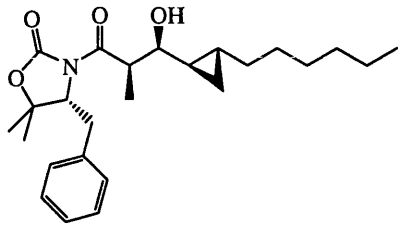
The title compound was prepared as the general procedure. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* recrystallisation (Et_2O, hexane) gave **147h** as a white solid in 99% yield; R_f (CH_2Cl_2) = 0.30; $[\alpha]_D^{25}$ = +8 (c = 0.66, CH_2Cl_2); mp = 105-108°C (Et_2O, hexane); δH (300 MHz, $CDCl_3$) 7.28-7.14 (5H, m, Ph) 4.47 (1H, dd, J = 9.0 Hz and 4.5 Hz, CHN), 3.89 (1H, qd, J = 7.0 Hz and 3.5 Hz, COCH), 3.47 (1H,dd, J = 9.5 Hz and 3.5 Hz, C*H*OH), 3.03 (1H, dd, J = 14.0 Hz and 4.5 Hz, CH_AH_BPh), 2.83 (1H, dd, J = 14.0 and 9.0 Hz, CH_ACH_BPh), 2.69 (1H, broad s, OH), 1.32 (3H, s, (CH_3)C(CH_3)), 1.31 (3H, s, (CH_3)C(CH_3)), 1.18 (3H, d, J = 7.0 Hz, CH_3CH), 1.01 (3H, s, (CH_3)(CH_3)-cyclopropane), 0.98 (3H, s, (CH_3)(CH_3)-cyclopropane), 0.77 (1H, app. td, J = 8.5 Hz and 5.5 Hz, cyclopropyl-CH), 0.51 (1H, dd, J = 8.5 Hz and 4.0 Hz, cyclopropyl-CH_AH_B), 0.25 (1H, app. t, J = 5 Hz, cyclopropyl-CH_AH_B); δC (75MHz, $CDCl_3$) 177.6, 152.8, 137.1, 129.5, 129.1, 127.3, 82.6, 73.1, 63.9, 43.2, 35.8, 28.8, 27.8, 27.6, 23.1, 22.0, 19.5, 18.9, 11.7; IR (KBr / cm^{-1}) 3515 (broad O-H), 1781 ($C=O_{ox}$), 1685 (C=O); LRMS : m/z (CI) 455.2 (40%) $[M+NH_4]^+$, 438.3 (40%) $[M+H]^+$; HRMS: m/z (ES) $[M+NH_4]^+$ requires 377.2435, found 377.2434.

3.7.8 (*S*)-4-Benzyl-3-[(2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*S*)-2-methyl-cyclopropyl)-propionyl]-5,5-dimethyl-oxazolidin-2-one 147g



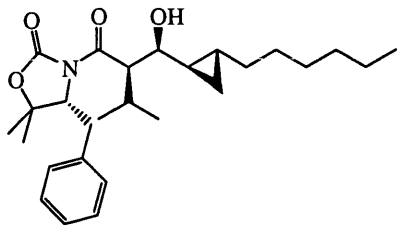
The title compound was prepared as the general procedure. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* recrystallisation (Et_2O, hexane) gave **147g** as a white solid in 95% yield; R_f (CH_2Cl_2) = 0.21; $[\alpha]_D^{25}$ = +6 (c = 0.86, CH_2Cl_2); mp = 98-101°C (Et_2O, hexane); δH (300 MHz, $CDCl_3$) 7.39-7.19 (5H, m, Ph) 4.54 (1H, dd, J = 9.0 Hz and 4.0 Hz, CHN), 4.00 (1H, qd, J = 7.0 Hz and 3.5 Hz, COCH), 3.21 (1H, dd, J = 8.5 Hz and 3.5 Hz, C*H*OH), 3.09 (1H, dd, J = 14.5 Hz and 4.0 Hz, CH_AH$_B$Ph), 2.91 (1H, dd, J = 14.5 and 9.0 Hz, CH$_A$CH_BPh), 2.47 (1H, broad s, OH), 1.39 (3H, s, (CH_3)C(CH$_3$)), 1.38 (3H, s, (CH$_3$)C(CH_3)), 1.26 (3H, d, J = 7.0 Hz, CH_3CH), 1.04 (3H, s, CH_3-cyclopropane), 0.78-0.63 (2H, m, CH$_3$-cyclopropyl-C*H* and CH-cyclopropyl-C*H*), 0.53 (1H, app. dt, J = 8.5 Hz and 4.5 Hz, cyclopropyl-CH_AH$_B$), 0.33 (1H, app. dt, J = 8.0 Hz and 5.0 Hz, cyclopropyl-CH$_A$$H_B$); δC (75MHz, $CDCl_3$) 176.7, 152.5, 136.7, 129.1, 128.7, 126.9, 82.2, 76.6, 76.1, 63.5, 42.9, 35.4, 28.5, 23.1, 22.2, 18.3, 11.5, 10.9; IR (KBr / cm^{-1}) 3488 (broad O-H), 1778 (C=O$_{ox}$), 1687 (C=O); HRMS: m/z (ES) $[M+NH_4]^+$ requires 363.2278, found 363.2281.

3.7.9 (*R*)-4-Benzyl-3-[(2*R*,3*S*)-3-((1*R*,2*R*)-2-hexyl-cyclopropyl)-3-hydroxy-2-methyl-propionyl]-5,5-dimethyl-oxazolidin-2-one 180b



The title compound was prepared as the general procedure from the from *ent*-**130**. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **180b** as a yellow oil in 93% yield; R_f (CH_2Cl_2) = 0.31; $[\alpha]_D^{25}$ = -5 (c = 0.89, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.29-7.11 (5H, m, Ph), 4.46 (1H, dd, J = 9.0 Hz and 4.0 Hz, CHN), 3.92 (1H, qd, J = 7.0 Hz and 3.0 Hz, COCH), 3.15 (1H, dd, J = 8.5 Hz and 3.0 Hz, C*H*OH), 3.03 (1H, dd, J = 14.5 and 4.0 Hz, CH_AH$_B$Ph), 2.83 (1H, dd, J = 14.5 and 9.0 Hz, CH$_A$CH_BPh), 2.47 (1H, broad s, OH), 1.32 (3H, s, (CH_3)C(CH$_3$)), 1.30 (3H, s, (CH$_3$)C(CH_3)), 1.30-1.06 (12H, m, alkyl-C_6H_{12}), 1.20 (3H, d, J = 7.0 Hz, CH_3CH), 0.81 (3H, t, J = 7.0 Hz, alkyl-CH$_3$), 0.68 (1H, m, CH-cyclopropyl-C*H*), 0.60 (1H, m, alkyl-cyclopropyl-C*H*), 0.46 (1H, app. dt, J = 8.5 Hz and 4.5 Hz, cyclopropyl-CH_AH$_B$), 0.29 (1H, app. dt, J = 8.0 Hz and 3.0 Hz, cyclopropyl-CH$_A$$H_B$); δC (75MHz, $CDCl_3$) 177.4, 152.8, 137.1, 129.5, 129.1, 127.3, 82.6, 76.2, 63.9, 43.2, 35.8, 34.0, 32.3, 29.8, 29.6, 28.9, 23.1, 22.7, 22.3, 17.0, 14.5, 11.6, 11.1; IR (film / cm^{-1}) 3531 (broad OH), 1779 (C=O$_{ox}$), 1699 (C=O); HRMS: m/z (EI) $[M]^+$ requires 415.2717, found 415.2720.

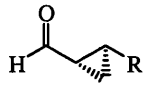
3.7.10(*R*)-4-Benzyl-3-{(*R*)-2-[(*S*)-((1*R*,2*R*)-2-hexyl-cyclopropyl)-hydroxy-methyl]-3-methyl-butyryl}-5,5-dimethyl-oxazolidin-2-one 182b



The title compound was prepared as the general procedure from *ent*-**181**. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **182b** as a yellow oil in 94% yield; R_f (CH_2Cl_2) = 0.41; $[\alpha]_D^{25}$ = -21 (c = 0.62, MeOH); δH (300 MHz, $CDCl_3$) 7.34-7.18 (5H, m, Ph), 4.56 (1H, dd, J = 10.0 Hz and 3.5 Hz, CHN), 4.22 (1H, dd, J = 8.5 and 6.0 Hz, COCH), 3.39 (1H, dd, J = 8.5 Hz and 6.0 Hz, C*H*OH), 3.23 (1H, dd, J = 14.5 and 3.5 Hz, CH_AH$_B$Ph), 2.86 (1H, dd, J = 14.5 Hz and 10.0 Hz, CH$_A$CH_BPh), 2.31 (1H, m, isopropyl-CH), 1.85 (1H, broad s, OH), 1.44-1.20 (10H m, alkyl-C_5H_{10}), 1.34 (3H, s, (CH_3)C(CH$_3$)), 1.33 (3H, s, (CH$_3$)C(CH_3)), 1.02 (3H, d, J = 7.0 Hz, isopropyl-CH$_3$), 1.00 (1H, obs. m, CH-cyclopropyl-C*H*), 0.93 (3H, d, J = 7.0 Hz, isopropyl-CH$_3$), 0.88 (3H, t, J = 7.0 Hz, alkyl-CH$_3$), 0.76 (1H, m, alkyl-cyclopropyl-C*H*), 0.43 (1H, app. dt, J = 8.5 Hz and 4.5 Hz, cyclopropyl-CH_AH$_B$), 0.28 (1H, app. dt, J = 8.5 Hz and 5.0 Hz, cyclopropyl-CH$_A$$H_B$); δC (75MHz, $CDCl_3$) 175.1, 153.7, 137.5, 129.4, 129.1, 127.2, 82.2, 75.5, 64.4, 54.5, 35.8, 34.2, 32.3, 29.6, 29.5, 28.8, 28.6, 23.1, 22.8, 22.2, 21.4, 21.1, 18.8, 14.5, 9.6; IR (film / cm^{-1}) 3516 (broad O-H), 1778 (C=O$_{ox}$), 1693 (C=O); HRMS: m/z (ES) [M+NH$_4$]$^+$ requires 461.3374 found 461.3370.

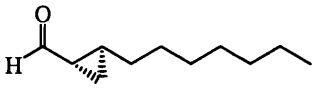
Chapter 3.8 General procedure for the anionic *retro*-aldol reaction of α-methyl cyclopropyl *syn*-aldols

3.8.1 General procedure



To a stirred solution of *syn*-aldol (1 equivalent) in dry toluene (10 cm^3) under nitrogen, LHMDS (1.1 equivalents, 1 mol dm^{-3} solution in THF) was added in one portion at -10°C to 10°C depending on specific substrate and stirred for 2 hours. The reaction was quenched dropwise with a cooled solution of saturated aqueous ammonium chloride solution (5 cm^3) and allowed to warm to room temperature over a period of thirty minutes. Saturated aqueous sodium hydrogen carbonate solution was added, sufficient to dissolve the resulting white precipitate. The mixture was extracted with dichloromethane (3 x 10 cm^3), washed with brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product, which was purified by silica gel chromatography.

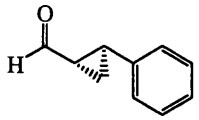
3.8.2 (1*S*,2*S*)-2-heptylcyclopropanecarbaldehyde 148b



The title compound was prepared as the general procedure from **147b**. The *retro*-aldol reaction was optimised at 10°C. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, Et_2O:Pentane, 2:98) gave **148b** as a yellow oil in 73% yield; R_f (Et_2O:Pentane, 2:98) = 0.71; $[\alpha]_D^{25}$ = +45 (c = 1.22, $CHCl_3$); δH (300 MHz,

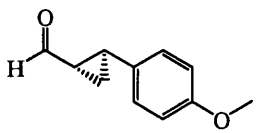
$CDCl_3$) 9.00 (1H, d, J = 5.5 Hz, CHO), 1.62 (1H, m, CHO-cyclopropyl-C*H*), 1.51-1.18 (13H, m, alkyl-C_6H_{12} and alkyl-cyclopropyl-C*H*), 0.95-0.82 (5H, t and m, J = 7.0 Hz, alkyl-CH_3 and cyclopropyl-CH_2); δC (75MHz, $CDCl_3$) 201.4, 35.0, 32.2, 30.9, 29.6, 29.5, 29.4, 23.1, 23.0, 15.3, 14.5; IR (film / cm^{-1}) 1710 (C=O); HRMS : m/z (EI) $[M-H]^+$ requires 167.1430, found 167.1427.

3.8.3 (1*S*,2*S*)-2-phenylcyclopropanecarbaldehyde 148a



The title compound was prepared as the general procedure from **147a**. The *retro*-aldol reaction was optimised at 10°C. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, Et_2O:Pentane, 2:98) gave **148a** as a yellow oil in 75% yield; R_f (Et_2O:Pentane, 2:98) = 0.38; $[\alpha]_D^{25}$ = +392 (c = 1.44, $CHCl_3$); δH (300 MHz, $CDCl_3$) 9.33 (1H, d, J = 5.0 Hz, CHO), 7.34-7.09 (5H, m, Ph), 2.63 (1H, ddd, J = 11.0 Hz, 7.0 Hz and 5.0 Hz, Ph-cyclopropyl-C*H*), 2.18 (1H, m, CHO-cyclopropyl-C*H*), 1.74 (1H, app. dt, J = 10.0 Hz and 5.0 Hz, cyclopropyl-CH_AH_B), 1.54 (1H, ddd, J = 8.5 Hz, 7.0 Hz and 5.0 Hz); δC (75MHz, $CDCl_3$) 200.2, 139.4, 129.0, 127.3, 126.7, 34.2, 27.0, 16.9; IR (film / cm^{-1}) 1699 (C=O); HRMS : m/z (ES) $[M+NH_4]^+$ requires 164.1070, found 164.1069.

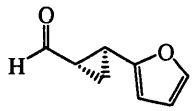
3.8.4 (1*S*,2*S*)-2-(4-methoxyphenyl)cyclopropanecarbaldehyde 148c



The title compound was prepared as the general procedure from **147c**. The *retro*-aldol reaction was optimised at 10°C. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, Et_2O:Pentane, 10:98) gave **148c** as a yellow oil in 63% yield;

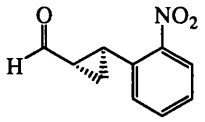
R_f (Et_2O:Pentane, 10:98) = 0.30; $[\alpha]_D^{25}$ = +228 (c = 0.36, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 9.23 (1H, d, J = 4.5 Hz, CHO), 6.95 (2H, d, J = 8.5 Hz, MeOCHC*H*C), 6.76 (2H, d, J = 8.5 Hz, MeOC*H*CHC), 3.72 (3H, s, CH_3O), 2.53 (1H, ddd, J = 9.0 Hz, 7.0 Hz and 4.0 Hz, MeOPh-cyclopropyl-CH), 2.02 (1H, m, CHO-cyclopropyl-C*H*), 1.63 (1H, app. dt, J = 9.5 Hz and 5.0 Hz, cyclopropyl-CH_AH_B), 1.41 (1H, ddd, J =11.5 Hz, 7.0 Hz and 5.0 Hz); δC (75MHz, $CDCl_3$) 200.2, 159.0, 131.3, 127.9, 114.4, 55.7, 34.1, 26.5, 16.6; IR (film / cm^{-1}) 1698 (C=O), 1517 (MeO); HRMS: m/z (ES) $[M+H]^+$ requires 177.0910 found 177.0910.

3.8.5 (1*S*,2*S*)-2-(furan-2-yl)cyclopropanecarbaldehyde 148e



The title compound was prepared as the general procedure from **147e**. The *retro*-aldol reaction was optimised at 10°C. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, Et_2O:Pentane, 10:90) gave **148e** as a yellow oil in 71% yield; R_f (Et_2O:Pentane, 10:90) = 0.69; $[\alpha]_D^{25}$ = +320 (c = 0.50, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 9.30 (1H, d, J = 4.0 Hz, CHO), 7.20 (1H, dd, J = 2.0 Hz and 1.0 Hz, furyl-OCH), 6.23 (1H, dd, J = 3.0 Hz and 3.0 Hz, furyl-OCHC*H*), 6.04 (1H, m, furyl-OCCH), 2.55 (1H, ddd, J = 9.0 Hz, 7.0 Hz and 4.0 Hz, furan-cyclopropyl-CH), 2.22 (1H, app. ddt, J = 8.5 Hz, 5.5 Hz and 4.0 Hz, CHO-cyclopropyl-C*H*), 1.59 (1H, m, cyclopropyl-CH_AH_B), 1.52 (1H, ddd, J =8.5 Hz, 6.5 Hz and 5.0 Hz); δC (75MHz, $CDCl_3$) 199.7, 152.8, 141.8, 111.0, 106.21, 31.7, 20.5, 15.0; IR (film / cm^{-1}) 1694 (C=O); HRMS : m/z (EI) $[M]^+$ requires 136.0519, found 136.0517.

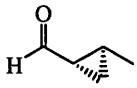
3.8.6 (1*S*,2*S*)-2-(2-nitrophenyl)cyclopropanecarbaldehyde 148d



The title compound was prepared as the general procedure from **147d**. The *retro*-aldol reaction was optimised at 10°C. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, Et_2O:Pentane, 10:90) gave **148d** as a yellow oil in 53% yield; R_f (Et_2O:Pentane, 10:90) = 0.25; $[\alpha]_D^{25}$ = +109 (c = 0.68, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 9.38 (1H, d, J = 4.5 Hz, CHO), 7.97 (1H, dd, J = 8.0 Hz and 1.0 Hz, NO_2CCH), 7.57 (1H, app. dt, J = 8.0 Hz and 2.0 Hz, NO_2C-*p*-CH), 7.42 (1H, app. dt, J = 8.5 Hz and 1.5 Hz, NO_2CCCH), 7.28 (1H, app. d, J = 9.0 Hz, NO_2CCHCH), 3.11 (1H, ddd, J = 8.5 Hz, 7.0 Hz and, 4.0 Hz, NO_2Ph-cyclopropyl-CH), 2.12 (1H, m, CHO-cyclopropyl-C*H*), 1.79 (1H, app. dt, J = 9.5 Hz and 5.5 Hz, cyclopropyl-CH_AH_B) 1.51 (1H, ddd, J = 8.5 Hz, 7.0 Hz and 5.5 Hz, cyclopropyl-CH_AH_B); δC (75MHz, $CDCl_3$) 194.4, 150.8, 134.2, 133.6, 129.5, 128.5, 125.3, 32.0, 24.1, 15.2; IR (film / cm^{-1}) 1708 (C=O), 1519 (NO_2), 1344 (NO_2); HRMS : m/z (EI) $[M]^+$ requires 191.0577 found, 191.0572.

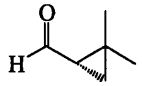
Chapter 3.9 General procedures for the preparation of volatile cyclopropane carboxaldehydes

3.9.1 (1*S*,2*S*)-2-methylcyclopropanecarbaldehyde 148g



LHMDS (1.1 equivalents, 1 mol dm^{-3} solution in toluene-d^8) was added in one portion to a stirred solution of **147g** (1 equivalent) in dry toluene-d^8 (5 cm^3) at 10°C under nitrogen. The reaction was stirred for 2 hours and was then quenched dropwise with the minimum amount of a cooled solution of saturated aqueous ammonium chloride solution (5 drops) and the mixture was allowed to warm to room temperature over a period of thirty minutes. The reaction mixture was dried (3Å molecular sieves), filtered, and the filtrate washed with toluene-d^8 (1 cm^3). The resulting mixture was distilled at atmospheric pressure (120°C) to give **148g** as solution in toluene-d^8. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. The concentration of the resulting solution was determined by the addition of a known of amount of 2,4-dimethylfuran as an internal standard to ^{1}H-NMR spectrum and comparing the intensities of the relevant integrals, to give **148g** in 51% yield; $[\alpha]_D^{25}$ = +54 (c = 0.71, toluene-d^8); δH (300 MHz, Toluene-d^8) 8.67 (1H, d, J = 5.0 Hz, CHO), 1.11 (1H, app. sextet, J = 4.5 Hz, CHO-cyclopropyl-C*H*), 0.98-0.87 (2H, m, CH_3-cyclopropyl-C*H* and cyclopropyl-CH_AH_B), 0.80 (1H, m, cyclopropyl-CH_AH_B), 0.67 (3H, d, J = 6.0 Hz, CH_3); δC (75MHz, Toluene-d^8) 197.3, 29.9, 15.8, 14.8, 14.0.

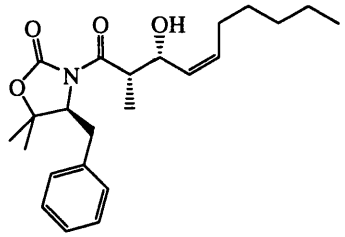
3.9.2 (*S*)-2,2-Dimethylcyclopropanecarbaldehyde 148h



LHMDS (1.1 equivalents, 1 mol dm^{-3} solution in toluene-d^8) was added in one portion at 10°C to a stirred solution of **147h** (1 equivalent) in dry toluene-d^8 (5 cm^3), under nitrogen. The reaction was stirred for 2 hours and was then quenched dropwise with the minimum amount of a cooled solution of saturated aqueous ammonium chloride solution (5 drops) and allowed to warm to room temperature over a period of thirty minutes. The reaction mixture was dried (3Å molecular sieves), filtered, and the filtrate washed with toluene-d^8 (1 cm^3). The resulting mixture was distilled at atmospheric pressure (130°C) to give **148h** as solution in toluene-d^8. The concentration of the resulting solution was determined by the addition of a known of amount of 2,4-dimethylfuran as an internal standard to ^{1}H-NMR spectrum, by comparing the intensities of the relevant integrals, to give **148h** in 61% yield; the enantiomeric excess was determined as >95% ee by derivatisation of the aldehyde with chirally pure (1*R*,2*R*)-N^1,N^2-dimethyl-1,2-diphenylethane-1,2-diamine **151** and examination of the crude 300 MHz ^{1}H-NMR spectrum; $[\alpha]_D^{25}$ = +63 (c = 1.22, toluene-d^8); δH (300 MHz, Toluene-d^8) 9.13 (1H, d, J = 5.0 Hz, CHO), 1.11 (1H, qd, J = 8.0 Hz and 5.0 Hz, CHO-cyclopropyl-C*H*), 0.96 (1H, obs. m, cyclopropyl-CH_AH_B), 0.94 (3H, s, (CH_3)(CH$_3$)-cyclopropane), 0.75 (3H, s, (CH$_3$)(CH_3)-cyclopropane), 0.50 (1H, dd J = 8.0 Hz and 4.5 Hz, cyclopropyl-CH_AH_B); δC (75MHz, Toluene-d^8) 197.6, 34.9, 25.8, 23.9, 21.3, 15.8.

Chapter 3.10 General procedures for the preparation of *cis*-cyclopropane carboxaldehyde

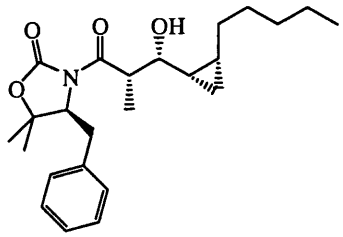
3.10.1 (*S*)-4-Benzyl-3-((*Z*)-(2*S*,3*R*)-3-hydroxy-2-methyl-dec-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 137f



(*S*)-4-Benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-dec-4-ynoyl)-5,5-dimethyl-oxazolidin-2-one **138** was dissolved in dry methanol (10 cm^3), Lindlar's catalyst (10 mol%) was added and stirred for 5 minutes. The heterogeneous mixture was purged with a balloon of hydrogen three times before being kept under hydrogen (1 atm.) and vigorously stirred, such as to generate a deep vortex in the solution. After one hour, or when thin layer chromatography had shown complete consumption of the starting material, the hydrogen balloon was removed and the reaction mixture was filtered through Celite with dichloromethane (3 x 10 cm^3) as eluent. The solvent was removed under reduced pressure to give the crude product. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. The *cis*-stereochemistry of the olefin functionality was determined from literature precedent and the alkene protons coupling constant (J_{cis} = 11 Hz). Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave the title compound **137f** as a yellow oil in 95% yield; R_f (CH_2Cl_2) = 0.41; $[\alpha]_D^{25}$ = -27 (c = 0.70, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.27-7.12 (5H, m, Ph), 5.48 (1H, dtd, J = 11.0 Hz, 7.0 Hz and 1.0 Hz, CH=C*H*C_5H_{11}), 5.36 (1H, ddt, 11.0 Hz, 8.5 Hz and 1.5 Hz, C*H*=CHC_5H_{11}), 4.62 (1H, dd, J = 8.5 Hz and 5.0 Hz, C*H*OH), 4.45 (1H, dd, J = 9.0 and 4.5 Hz, CHN), 3.89

(1H, qd, J = 7.0 and 5.0 Hz, COCH), 3.00 (1H, dd, J = 14.5 and 4.5 Hz, C*H*$_A$H$_B$Ph), 2.83 (1H, dd, J = 14.5 and 9.0 Hz, CH$_A$C*H*$_B$Ph), 2.28 (1H, broad s, OH), 2.01 (2H, m, CH=CHC*H*$_2$), 1.33-1.17 (6H, obs. m, alkyl-C$_3$H$_6$), 1.32 (3H, s, (C*H*$_3$)C(CH$_3$)), 1.31 (3H, s, (CH$_3$)C(C*H*$_3$)), 1.12 (3H, d, J = 7.0 Hz, C*H*$_3$CH), 0.82 (3H, t, J = 7.0 Hz, alkyl-CH$_3$); δC (75MHz, CDCl$_3$) 176.6, 152.9, 137.1, 131.4, 129.6, 129.1, 128.9, 127.2, 82.6, 69.0, 64.0, 43.5, 35.9, 32.0, 29.6, 29.5, 28.2, 22.9, 22.6, 14.4, 12.7; IR (film / cm^{-1}) 3497 (broad OH), 1778 (C=O$_{ox}$), 1698 (C=O); HRMS: m/z (ES) [M+NH$_4$]$^+$ requires 405.2748, found 405.2749.

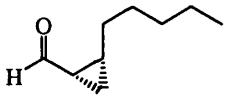
3.10.2(*S*)-4-Benzyl-3-[(2*S*,3*R*)-3-hydroxy-2-methyl-3-((1*S*,2*R*)-2-pentyl-cyclopropyl)-propionyl]-5,5-dimethyl-oxazolidin-2-one 147f



Diethyl zinc (5 equivalents, 1.0 mol dm^{-3} solution in hexane) was added in one portion *via* syringe to a stirred solution of **137f** (1 equivalent) in dry dichloromethane at -10°C, before the immediate addition of diiodomethane (5 equivalents) in one portion *via* syringe, under nitrogen and in the absence of light. The solution was allowed to warm to 0°C over 2 hours before being quenched with saturated sodium sulfite solution (5 cm^3) and stirred for 10 minutes. Hydrochloric acid (1.0 mol dm^{-3} solution in water) was added, sufficient to dissolve the white precipitate. The crude product was extracted with dichloromethane (3 x 10 cm^3), washed with brine (10 cm^3) and dried (MgSO$_4$). The solvent was removed under reduced pressure to give the crude product. The all-*syn* stereochemistry was assigned as drawn due to literature precedent and the minimisation the A^{1,3}-strain in the transition state. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO$_2$, CH$_2$Cl$_2$)

gave **147f** as a yellow oil in 96% yield; R_f (CH_2Cl_2) = 0.44; $[\alpha]_D^{25}$ = -29 (c = 0.69, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.34-7.19 (5H, m, Ph), 4.53 (1H, dd, J = 9.0 Hz and 4.5 Hz, CHN), 3.95 (1H, qd, J = 7.0 and 3.0 Hz, COCH), 3.55 (1H, app. dt, J = 9.0 Hz and 3.0 Hz, C*H*OH), 3.09 (1H, dd, J = 14.5 and 4.5 Hz, CH_AH_BPh), 2.91 (1H, dd, J = 14.5 and 9.0 Hz, CH_ACH_BPh), 2.74 (1H, d, J = 2.5 Hz, OH), 1.63-1.21 (8H, obs. m, alkyl-C_4H_8), 1.40 (3H, s, (CH_3)C(CH_3)), 1.37 (3H, s, (CH_3)C(CH_3)), 1.29 (3H, d, J = 7.0 Hz, CH_3CH), 1.07-0.93 (2H, m, cyclopropyl-CH), 0.88 (3H, t, J = 7.0 Hz, alkyl-CH_3), 0.86-0.76 (1H, m, cyclopropyl-CH_2); δC (75MHz, $CDCl_3$) 177.9, 152.7, 137.1, 129.5, 129.1, 127.3, 82.6, 72.4, 70.0, 43.8, 35.8, 32.1, 30.2, 29.3, 28.8, 28.1, 22.6, 19.4, 16.7, 15.0, 11.6, 10.2; IR (film / cm^{-1}) 3522 (broad O-H), 1779 ($C=O_{ox}$), 1703 (C=O); HRMS: m/z (ES) $[M+H]^+$ requires 402.2639, found 402.2637.

3.10.3(1*S*,2*R*)-2-pentylcyclopropanecarbaldehyde 148f

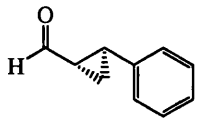


LHMDS (1.1 equivalents, 1 mol dm^{-3} solution in THF) was added in one portion to a stirred solution of **147f** (1 equivalent) in dry toluene (10 ml) at 0°C, under nitrogen. The reaction mixture was stirred for 2 hours and was then quenched dropwise with a cooled solution of saturated aqueous ammonium chloride solution (5 cm^3) and allowed to warm to room temperature over a period of 30 minutes. Saturated aqueous sodium hydrogen carbonate solution was added, sufficient to dissolve the white precipitate. The resulting mixture was extracted with dichloromethane (3 x 10 cm^3), washed with brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, Et_2O, Pentane) gave **148f** as a yellow oil in 61% yield; R_f (Et_2O:Pentane, 3:97) = 0.31; $[\alpha]_D^{25}$ = -10 (c = 1.01, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 9.35 (1H, d, J = 5.5 Hz, CHO), 1.62 (1H, m, CHO-cyclopropyl-C*H*), 1.51-1.18 (13H, m, alkyl-C_6H_{12} and alkyl-cyclopropyl-C*H*), 0.95-0.82 (5H, t and m, J = 7.0 Hz, alkyl-CH_3 and cyclopropyl-CH_2); δC (75MHz, $CDCl_3$) 200.8,

30.4, 29.5, 28.6, 27.2, 23.8, 21.6, 13.7, 13.0; IR (film / cm^{-1}) 1704 (C=O). HRMS: No molecular ion found

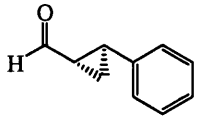
Chapter 3.11 Representative procedures for alternative *retro*-aldol reactions

3.11.1 High temperature thermal *retro*-aldol reaction of (1*S*,2*S*)-2-Phenylcyclopropanecarbaldehyde 148a



In a Kügelröhr, *syn*-aldol **147a** was heated to 220°C under reduced pressure (400 mb) for 1 hour. The aldehyde was distilled directly from the reaction mixture and collected in the second bulb of the Kügelröhr (0°C), to afforded spectroscopically pure **148a** in 93% yield, which matched the previously described data for this compound. The first bulb contained spectroscopically pure (*S*)-4-benzyl-5,5-dimethyl-3-propionyloxazolidin-2-one **130** in 91% yield, which matched the previously described data for this compound.

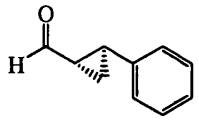
3.11.2 Surface catalysed thermal *retro*-aldol reaction of (1*S*,2*S*)-2-Phenylcyclopropanecarbaldehyde 148a



Silica or activated carbon (20 mol%) was added to a solution of *syn*-aldol **147a** (1 equivalent) in toluene (10 cm^3) and the mixture was refluxed for 8 hours or when thin layer chromatography indicated that all the starting material had been consumed. The mixture was allowed to cool to room temperature and filtered through Celite with ethyl acetate as eluent (3 x 10 cm^3). The solvent was removed under reduced pressure, which gave the crude product. The diastereomeric excess was determined as

>95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, Et_2O:Pentane, 3:97) gave **148a** as a yellow oil in 81% yield, which matched the previously described data for this compound.

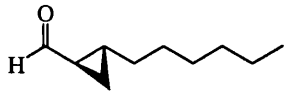
3.11.3 Samarium(II) iodide mediated *retro*-aldol reaction of (1*S*,2*S*)-2-Phenylcyclopropanecarbaldehyde 149c



Samarium(II) iodide (1.1 equivalents, 0.1 mol dm^{-3} solution in THF) was added dropwise over a 30 minute period to a solution of **147a** in dry degassed THF (10 cm^3) under nitrogen at room temperature, and the solution was stirred for 2 hours. The reaction was quenched with hydrochloric acid (5 cm^3, 1 mol dm^{-3} solution in water), extracted with ether (3 x 20 cm^3), washed with aqueous saturated sodium thiosulphate solution (5 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. Purification *via* column chromatography (SiO_2, Et_2O:Pentane, 3:97) gave **148a** as a yellow oil in 73% yield, which matched the previously described data for this compound.

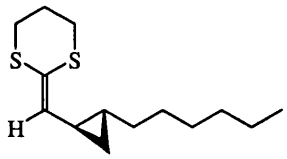
Chapter 3.12 General procedures for the asymmetric synthesis of *Cascarillic acid*

3.12.1 (1*R*,2*R*)-2-hexylcyclopropanecarbaldehyde 180c



KHMDS (1.1 equivalents, 0.5 mol dm^{-3} solution in toluene) was added dropwise to a solution of *syn*-aldol **182b** in dry THF under nitrogen at -40°C, and stirred for 2 hours. The reaction was quenched with saturated aqueous ammonium chloride solution (2 cm^3) and saturated aqueous sodium hydrogen carbonate solution, sufficient to dissolve the white precipitate. The solution was extracted with ether (3 x 10 cm^3), washed with brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, Et_2O:Pentane, 2:98) gave **180c** as a clear oil in 87% yield; R_f (Et_2O:Pentane, 3:97) = 0.31; $[\alpha]_D^{25}$ = -26 (c = 0.35, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 8.98 (1H, d, J = 5.5 Hz, CHO), 1.61 (1H, m, CHO-cyclopropyl-C*H*), 1.51-1.20 (11H, m, alkyl-cyclopropyl-C*H* and C_5H_{10}), 0.96-0.83 (5H, m, cyclopropyl-CH_2 and CH_3); δC (75MHz, $CDCl_3$) 201.2, 32.6, 31.7, 30.6, 29.0, 28.9, 22.7, 22.6, 14.9, 14.1; IR (Film / cm^{-1}) 1713 (C=O); HRMS : m/z (ES) $[M+NH_4]^+$ requires 172.1696, found 172.1696.

3.12.22-(((1*R*,2*R*)-2-hexylcyclopropyl)methylene)-1,3-dithiane 183



n-BuLi (1.02 equivalents, 2.5 mol dm^{-3} solution in hexane) was added in one portion to a solution of (1,3-dithian-2-yl)trimethylsilane (1.3 equivalents) in dry THF (5 cm^3) at 0°C under nitrogen and stirred for 1 hour. The reaction was then cooled to -30°C and (1*R*,2*R*)-2-hexylcyclopropanecarbaldehyde **180c** (1 equivalent) was added in one portion as a solution in dry THF (2 cm^3). The reaction was allowed to warm to room temperature over 2 hours, then quenched with aqueous saturated ammonium chloride solution (2 cm^3), extracted with ether (3 x 10 cm^3), washed with aqueous saturated sodium hydrogen carbonate solution (10 cm^3), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, Hexane:CH_2Cl_2, 95:5) gave **183** as a clear oil in 85% yield; R_f (Et_2O:Pentane, 3:97) = 0.31; $[\alpha]_D^{25}$ = -20 (c = 0.30, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 5.42 (1H, d, J = 10.0 Hz, CH=C), 2.91 (4H, m, 2 x SCH_2), 2.22-2.13 (2H, m, SCH_2CH_2), 1.58 (1H, m, cyclopropyl-C*H*CH=C), 1.41-1.20 (10H, m, alkyl-C_5H_{10}), 0.88 (3H, t, J = 7.0 Hz, alkyl-CH_3), 0.79 (1H, m, cyclopropyl-CH), 0.65-0.56 (2H, m, cyclopropyl-CH_2); δC (75MHz, $CDCl_3$) 140.4, 121.6, 34.1, 32.3, 31.3, 30.5, 29.7, 29.5, 26.0, 23.1, 22.2, 20.3, 15.2, 14.5; IR (Film / cm^{-1}) 1678 (C=C), (C-S); HRMS: m/z (ES) $[M+H]^+$ requires 257.1392, found 257.1393.

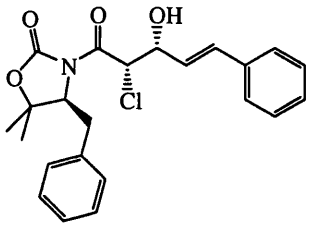
3.12.32-((1*S*,2*R*)-2-hexylcyclopropyl)acetic acid (*Cascarillic acid*) 177

para-Toluene sulphonic acid (10 mol%) was added in one portion to a solution of 2-(((1*R*,2*R*)-2-hexylcyclopropyl)methylene)-1,3-dithiane **183** (1 equivalent) in THF/water (8:1). The reaction was refluxed (75°C) for six hours, before cooling to room temperature. The volatile material was then removed under reduced pressure,

before the mixture was re-dissolved in acetone/water (8:1) and solid potassium hydroxide (5 equivalents) was added. The reaction was refluxed (85°C) for two hours, before cooling to room temperature. The reaction was then cautiously acidified with concentrated hydrochloric acid, extracted with ethyl acetate (3 x 10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, Hexane:Et_2O, 80:20), gave **177** as a clear oil in 73% yield, which matched the previously published data for this compound;[126] Rf (CH_2Cl_2) = 0.15; $[\alpha]_D^{25}$ = -11 (c = 0.41, $CHCl_3$); δH (300 MHz, $CDCl_3$) 2.26 (2H, app. d, J = 7.0 Hz, CH_2CO_2H), 1.41-1.18 (10H, m, alkyl-C_5H_{10}), 0.88 (3H, t, J = 7.0 Hz, alkyl-CH_3), 0.77 (1H, m, cyclopropyl-C*H*-CH_2CO_2H), 0.56 (1H, m, cyclopropyl-C*H*-C_6H_{13}), 0.33 (2H, m, cyclopropyl-CH_2) δC (75MHz, $CDCl_3$) 176.6, 37.5, 32.8, 30.9, 28.3, 28.1, 21.6, 17.7, 13.1, 13.0, 10.6; IR (Film / cm^{-1}) 1711 (C=O); HRMS : m/z (EI) $[M]^+$ requires 184.1458, found 184.1458.

Chapter 3.13 General procedures for the asymmetric synthesis of *Grenadamide*

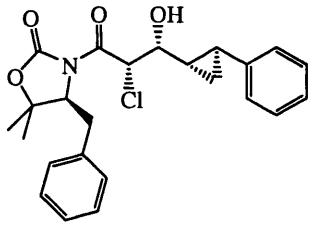
3.13.1(*S*)-4-Benzyl-3-((*E*)-(2*S*,3*R*)-2-chloro-3-hydroxy-5-phenyl-pent-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 195a



Dibutyl boron triflate (1.1 equivalents, of a 1.0 mol dm^{-3} solution in hexane) was added dropwise to a stirred solution of (*R*)-4-benzyl-3-(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one **166** (1 equivalent) in dry dichloromethane at 0°C under nitrogen. After 30 minutes, diisopropylethylamine (1.2 equivalents) was added a dropwise and the resulting solution stirred for a further 30 minutes. The solution was cooled to -78°C and (*E*)-cinnamaldehyde (1.1 equivalents) was added dropwise. The reaction was allowed to warm to room temperature overnight. The reaction was quenched with Na_2PO_4/NaH_2PO_4 buffer solution (pH7, 10 cm^3), and stirred for 10 minutes before the addition of 2:1 methanol-hydrogen peroxide solution (30%, 10 cm^3) and stirred for a further 2 hours. The mixture was extracted with dichloromethane (3 × 20 cm^3), washed with saturated aqueous sodium hydrogen carbonate solution (10 cm^3), brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. The relative and absolute stereochemistry was assumed as drawn from literature precedent and from the small α-proton coupling constant (5.5 Hz). The diastereomeric excess was determined as 92% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* recrystallisation (Et_2O, hexane) gave **195a** as a white solid in 83% yield and in >95%

de; m.p. = 173-176°C (Et_2O, hexane); R_f (CH_2Cl_2) = 0.21; $[\alpha]_D^{25}$ = +44 (c = 0.54, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.41-7.20 (10H, m, Ph), 6.72 (1H, d, J = 16.0, CH=C*H*Ph), 6.23 (1H, dd, 16.0 and 7.0 Hz, C*H*=CHPh), 5.84 (1H, d, J = 5.5 Hz, CHCl), 4.77 (1H, app. td, J = 7.0 Hz and 1.0 Hz, C*H*OH), 4.48 (1H, dd, J = 9.5 Hz and 4.0 Hz, CHN), 3.17 (1H, dd, J = 14.5 and 4.0 Hz, CH_AH_BPh), 2.92 (1H, dd, J = 14.5 and 9.5 Hz, CH_ACH_BPh), 2.82 (1H, broad s, OH), 1.37 (3H, s, $(CH_3)C(CH_3)$), 1.19 (3H, s, $(CH_3)C(CH_3)$); δC (75MHz, $CDCl_3$) 168.4, 152.3, 136.7, 136.2, 134.6, 129.5, 129.2, 129.0, 128.7, 127.4, 127.2, 125.9, 83.5, 73.6, 64.4, 59.7, 35.3, 28.7, 22.6; IR (KBr / cm^{-1}) 3468 (broad O-H), 1774 ($C=O_{ox}$), 1701 (C=O), 693 (C-Cl); HRMS : no molecular ion found.

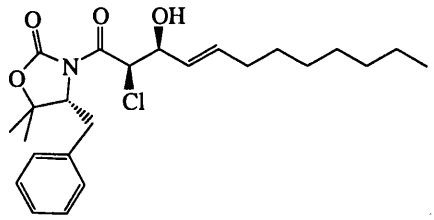
3.13.2(*S*)-4-Benzyl-3-[(2*S*,3*R*)-2-chloro-3-hydroxy-3-((1*S*,2*S*)-2-phenyl-cyclopropyl)-propionyl]-5,5-dimethyl-oxazolidin-2-one 195b



Diethyl zinc (5 equivalents, 1.0 mol dm^{-3} solution in hexane) was added in one portion *via* syringe to a stirred solution of (*R*)-4-Benzyl-3-((*E*)-(2*R*,3*S*)-2-chloro-3-hydroxy-dodec-4-enoyl)-5,5-dimethyl-oxazolidin-2-one **195a** (1 equivalent) in dry dichloromethane at -10°C, before the immediate addition of diiodomethane (5 equivalents) in one portion *via* syringe, under nitrogen and in the absence of light. The solution was allowed to warm to 0°C over 2 hours, before being quenched with saturated sodium sulfite solution (5 cm^3) and stirred for 10 minutes. Hydrochloric acid (1.0 mol dm^{-3} solution in water) was added, sufficient to dissolve the white precipitate. The crude product was extracted with dichloromethane (3 x 20 cm^3), washed with brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. The all-*syn* stereochemistry was assigned

as drawn due to literature precedent and by the minimisation the $A^{1,3}$-strain in the transition state. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **195b** as a yellow oil in 94% yield; R_f (CH_2Cl_2) = 0.17; $[\alpha]_D^{22}$ = +30 (c = 0.52, $CHCl_3$); δH (300 MHz, $CDCl_3$) 7.36-7.04 (10H, m, Ph), 5.88 (1H, d, J = 5.0 Hz, ClCH), 4.39 (1H, dd, J = 10.0 Hz and 4.0 Hz, CHN), 3.68 (1H, dd, J = 8.5 Hz and 5.5 Hz, C*H*OH), 3.22 (1H, dd, J = 14.5 Hz and 4.0 Hz, CH_AH$_B$Ph), 2.87 (1H, dd, J = 14.5 and 10.0 Hz, CH$_A$CH_BPh), 2.64 (1H, broad s, OH), 2.02 (1H, app. dt, J = 9.5 Hz and 5.5 Hz, Ph-cyclopropyl-C*H*), 1.48 (1H, m, CH-cyclopropyl-C*H*), 1.35 (3H, s, (CH_3)C(CH$_3$)), 1.19 (1H, app. dt, J = 9.0 Hz and 5.5 Hz, cyclopropyl-CH_AH$_B$) 1.0 (3H, s, (CH$_3$)C(CH_3)), 1.04 (1H, m, cyclopropyl-CH$_A$$H_B$); δC (75MHz, $CDCl_3$) 168.4, 152.3, 141.9, 136.8, 129.2, 128.9, 128.8, 127.4, 126.4, 125.9, 83.4, 75.5, 64.4, 60.2, 34.9, 28.5, 25.5, 22.7, 21.9, 15.5; IR (film / cm^{-1}) 3472 (broad OH), 1770 (C=O$_{ox}$), 1703 (C=O), 698 (C-Cl); HRMS : m/z (ES) [M+NH$_4$]$^+$ requires 445.1889, found 445.1885.

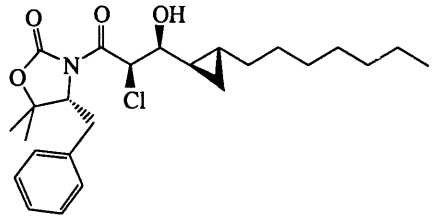
3.13.3(*R*)-4-Benzyl-3-((*E*)-(2*R*,3*S*)-2-chloro-3-hydroxy-dodec-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 195a



Dibutyl boron triflate (1.1 equivalents, of a 1.0 mol dm^{-3} solution in hexane) was added dropwise to a stirred solution of (*R*)-4-benzyl-3-(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one *ent*-**166** (1 equivalent) in dry dichloromethane at 0°C under nitrogen. After 30 minutes, diisopropylethylamine (1.2 equivalents) was added dropwise and the resulting solution stirred for a further 30 minutes. The solution was cooled to -78°C and (*E*)-dec-2-enal (1.1 equivalents) was added dropwise. The reaction was then allowed to warm to room temperature overnight. The reaction was

quenched with Na_2PO_4/NaH_2PO_4 buffer solution (pH7, 10 cm^3), and stirred for 10 minutes, before the addition of 2:1 methanol-hydrogen peroxide solution (30%, 10 cm^3) and stirred for a further 2 hours. The mixture was extracted with dichloromethane (3 × 20 cm^3), washed with saturated aqueous sodium hydrogen carbonate solution (10 cm^3), brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. The relative and absolute stereochemistry was assumed as drawn from literature precedent and from the small α-proton coupling constant (3.5 Hz). The diastereomeric excess was determined as 92% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **195a** as a yellow oil in 74% yield; R_f (CH_2Cl_2) = 0.36; $[\alpha]_D^{25}$ = +11 (c = 1.00, $CHCl_3$); δH (300 MHz, $CDCl_3$) 7.28-7.14 (5H, m, Ph), 5.79 (1H, dtd, J = 15.5 Hz, 6.5 Hz and 1.0 Hz, C*H*=CHCH$_2$), 5.65 (1H, d, J = 3.5 Hz, CHCl), 5.44 (1H, ddt, J = 15.5 Hz, 6.5 Hz and 1.5 Hz, CH=C*H*CH$_2$), 4.49 (1H, m, C*H*OH), 4.44 (1H, dd, J = 10.0 Hz and 4.0 Hz, CHN), 3.11 (1H, dd, J = 14.5 Hz and 4.0 Hz, CH_AH$_B$Ph), 2.85 (1H, dd, J = 14.5 Hz and 10.0 Hz, CH$_A$$H_B$Ph), 2.59 (1H, d, J = 3.5 Hz, OH), 1.98 (2H, m, CH=CHCH_2), 1.34 (3H, s, (CH_3)C(CH$_3$)), 1.29 (3H, s, (CH$_3$)C(CH_3)), 1.26-1.18 (10H, m, alkyl-C_5H_{10}), 0.81 (3H, t, J = 7.0 Hz, alkyl-CH$_3$); δC (75MHz, $CDCl_3$) 168.5, 152.3, 137.0, 136.7, 129.5, 129.2, 127.4, 126.7, 83.4, 73.2, 64.4, 59.8, 35.2, 32.7, 32.2, 29.5, 29.2, 28.9, 23.0, 22.6, 14.5; IR (Film / cm^{-1}) 3496 (broad O-H), 1778 (C=O_{ox}), 1708 (C=O), 1605 (C=C); HRMS : m/z (ES) $[M+NH_4]^+$ requires 453.2515, found 453.2515.

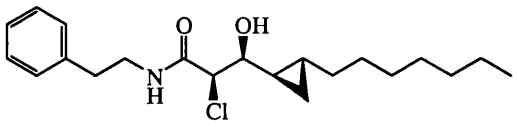
3.13.4 (*R*)-4-Benzyl-3-[(2*R*,3*S*)-2-chloro-3-((1*R*,2*R*)-2-heptyl-cyclopropyl)-3-hydroxy-propionyl]-5,5-dimethyl-oxazolidin-2-one 195b



Diethyl zinc (5 equivalents, 1.0 mol dm^{-3} solution in hexane) was added in one portion *via* syringe to a stirred solution of (*R*)-4-Benzyl-3-((*E*)-(2*R*,3*S*)-2-chloro-3-hydroxy-dodec-4-enoyl)-5,5-dimethyl-oxazolidin-2-one **195a** (1 equivalent) in dry dichloromethane at -10°C, before the immediate addition of diiodomethane (5 equivalents) in one portion *via* syringe, under nitrogen and in the absence of light. The solution was allowed to warm to 0°C over 2 hours, before being quenched with saturated sodium sulfite solution (5 cm^3) and stirred for 10 minutes. Hydrochloric acid (1.0 mol dm^{-3} solution in water) was added, sufficient to dissolve the white precipitate. The crude product was extracted with dichloromethane (3 x 20 cm^3), washed with brine (10 cm^3), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. The all-*syn* stereochemistry was assigned as drawn due to literature precedent and by the minimisation the $A^{1,3}$-strain in the transition state. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **195b** as a yellow oil in 98% yield; R_f (CH_2Cl_2) = 0.25; $[\alpha]_D^{25}$ = +11 (c = 1.00, $CHCl_3$); δH (300 MHz, $CDCl_3$) 7.32-7.17 (5H, m, Ph), 5.78 (1H, d, J = 3.0 Hz, C*H*Cl), 4.48 (1H, dd, J = 10.0 Hz and 3.5 Hz, CHN), 3.40 (1H, dd, J = 8.0 Hz and 3.0 Hz, C*H*OH), 3.20 (1H, dd, J = 14.5 Hz and 3.5 Hz, CH_AH_BPh), 2.87 (1H, dd, J = 14.5 Hz and 10.0 Hz, CH_AH_BPh), 2.61 (1H, broad s, OH), 1.36 (3H, s, (CH_3)C(CH_3)), 1.32 (3H, s, (CH_3)C(CH_3)), 1.27-1.12 (12H, m, alkyl-C_6H_{12}), 0.90 (1H, m, cyclopropyl-C*H*-CHOH), 0.85 (3H, t, J = 7.0 Hz, alkyl-CH_3), 0.79 (1H, m, cyclopropyl-C*H*-C_7H_{15})), 0.61 (1H, m, cyclopropyl-CH_AH_B), 0.40 (1H, m, cyclopropyl-CH_AH_B); δC (75MHz, $CDCl_3$) 168.3, 151.8, 136.4, 129.0, 128.7, 126.9,

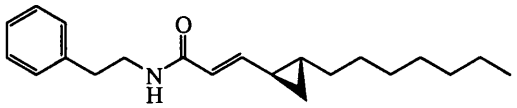
83.0, 75.1, 64.2, 60.6, 34.6, 33.4, 31.8, 29.4, 29.3, 29.2, 28.6, 22.6, 22.3, 21.7, 16.6, 14.0, 10.8; IR (Film / cm^{-1}) 3500 (broad O-H), 1770 ($C=O_{ox}$), 1716 (C=O); HRMS: m/z (ES) $[M+NH_4]^+$ requires 467.2671, found 467.2668.

3.13.5(2*R*,3*S*)-2-chloro-3-((1*R*,2*R*)-2-heptylcyclopropyl)-3-hydroxy-*N*-phenethylpropanamide 196



(*R*)-4-Benzyl-3-[(2*R*,3*S*)-2-chloro-3-((1*R*,2*R*)-2-heptyl-cyclopropyl)-3-hydroxy-propionyl]-5,5-dimethyl-oxazolidin-2-one **195b** was dissolved in neat phenylethylamine (5 cm^3) and stirred for 12 hours at room temperature. The crude reaction solution was then purified by column chromatography (SiO_2, EtOAc:Hexane; 20:80) to give **196** as a white solid in 89% yield. The diastereomeric excess was determined as >95% by examination of the 300 MHz ^{1}H-NMR spectrum. R_f (CH_2Cl_2) = 0.11; $[\alpha]_D^{25}$ = -23 (c = 1.00, $CHCl_3$); mp (EtOAc/Hexane) = 64-65°C; δH (300 MHz, $CDCl_3$) 7.34-7.18 (5H, m, Ph), 6.77 (1H, broad s, NH), 4.43 (1H, d, J = 2.5 Hz, C*H*Cl), 3.55 (1H, m, C*H*OH), 3.49 (2H, m, NCH_2), 2.83 (2H, m, CH_2Ph), 1.34-1.13 (12H, m, alkyl-C_6H_{12}), 0.88 (1H, m, cyclopropyl-C*H*-CHOH), 0.87 (3H, t, J = 7.0 Hz, alkyl-CH_3), 0.70 (1H, m, cyclopropyl-C*H*-C_7H_{15}), 0.59 (1H, m, cyclopropyl-CH_AH_B), 0.39 (1H, m, cyclopropyl-CH_AH_B); δC (75MHz, $CDCl_3$) 168.3, 138.8, 129.2, 129.0, 127.0, 76.3, 64.9, 41.5, 35.8, 33.8, 32.2, 29.8, 29.7, 23.0, 22.3, 17.2, 14.6, 11.3; IR (KBr / cm^{-1}) 3277 (broad O-H), 2921 (N-H), 1647 (C=O), 1557 (C-Cl); HRMS: m/z (ES) $[M+H]^+$ requires 366.2194, found 366.2198.

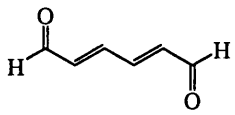
3.13.6(*E*)-3-((1*R*,2*R*)-2-heptylcyclopropyl)-*N*-phenethylacrylamide 197



Samarium(II) iodide (2.5 equivalents, 0.1 mol dm^{-3} solution in THF) was added in one portion to (2*R*,3*S*)-2-chloro-3-((1*R*,2*R*)-2-heptylcyclopropyl)-3-hydroxy-*N*-phenethylpropanamide **196** (1 equivalent) in dry degassed THF under nitrogen and stirred for 2 hours. The reaction was quenched with hydrochloric acid (5 cm^3, 1 mol dm^{-3} solution in water) and saturated sodium thiosulphate solution (5 cm^3), extracted with dichloromethane (3 x 10 cm^3), washed with brine (10 cm^3), dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **197** as a yellow oil in 85% yield; R_f (CH_2Cl_2) = 0.29; $[\alpha]_D^{25}$ = -37 (c = 0.99, $CHCl_3$); mp (EtOAc/Hexane) = 65-66°C; δH (300 MHz, $CDCl_3$) 7.34-7.16 (5H, m, Ph), 6.35 (1H, dd, J = 15.0 Hz and 10.0 Hz, COCH=C*H*), 5.71 (1H, d, J = 15.0 Hz, COC*H*=CH), 5.43 (1H, broad s, NH), 3.57 (2H, app. dd, J = 13.0 Hz and 7.0 Hz, CH_2NH), 2.83 (2H, app. t, J = 7.0 Hz, PhCH_2), 1.40-1.17 (13H, m, alkyl-C_6H_{12} and cyclopropyl-C*H*CH=CH), 0.94 (1H, m, cyclopropyl-C*H*-C_7H_{13}), 0.87 (3H, t, J = 7.2 Hz, alkyl-CH_3), 0.75 (1H, m, cyclopropyl-CH_AH_B), 0.67 (1H, m, cyclopropyl-CH_AH_B); δC (75MHz, $CDCl_3$) 166.5, 149.9, 139.4, 129.2, 129.0, 126.8, 120.0, 40.9, 36.1, 34.0, 32.2, 29.8, 29.7, 29.6, 23.2, 23.0, 22.2, 15.9, 14.5; IR (KBr / cm^{-1}) 2923 (broad N-H), 1663 (C=O), 1547 (C=C); HRMS: m/z (ES) $[M+H]^+$ requires 314.2477, found 314.2478.

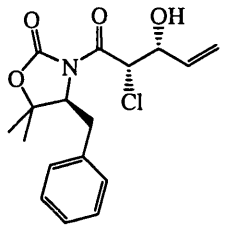
Chapter 3.14 General procedures for the asymmetric synthesis of oligomeric cyclopropanes

3.14.1 Mucanaldehyde 216



Diphenyl phosphanylidene acetaldehyde (1.9 equivalents) was added in one portion to a solution of glyoxal in DMF and heated to 80°C for two hours. The reaction was then cooled to room temperature and the crude mixture was pushed through a plug of silica (2 cm^3) with ether (10 cm^3) as eluent. The volatile materials were removed under reduced pressure and the crude DMF solution dissolved in toluene (10 cm^3), washed with distilled water (3 x 20 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure to give the crude product, The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, CH_2Cl_2) gave **216** as a yellow solid in 62% yield, which matched the previously published data for the compound;[159] R_f (CH_2Cl_2) = 0.17; mp = decomposed >50°C (CH_2Cl_2) δH (300 MHz, $CDCl_3$) 9.72 (2H, d, J = 7.5 Hz, CHO), 7.28 (2H, m, CHOCH=C*H*), 6.51 (2H, m, CHOC*H*=CH), δC (75MHz, $CDCl_3$) 191.4, 145.3, 137.0; IR (KBr / cm^{-1}) 1675 (C=O).

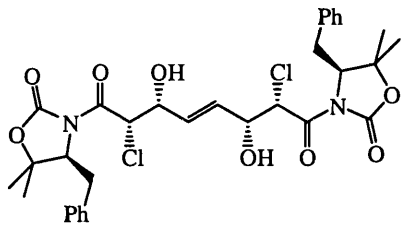
3.14.2(*S*)-4-Benzyl-3-((2*S*,3*R*)-2-chloro-3-hydroxy-pent-4-enoyl)-5,5-dimethyl-oxazolidin-2-one 223



Dibutyl boron triflate (1.1 equivalents, of a 1.0 mol dm^{-3} solution in hexane) was added dropwise to a stirred solution of (*S*)-4-benzyl-3-(2-chloroacetyl)-5,5-dimethyloxazolidin-2-one **166** (1 equivalent) in dry dichloromethane at 0°C, under nitrogen. After 30 minutes, diisopropylethylamine (1.2 equivalents) was added dropwise and the resulting solution stirred for a further 30 minutes. The solution was cooled to -78°C and acrolein (1.1 equivalents, 90% solution) was added dropwise. The reaction was allowed to warm to 0°C over two hours. The reaction was quenched with Na_2PO_4/NaH_2PO_4 buffer solution (pH7, 10 cm^3), and stirred for 10 minutes before the addition of 2:1 methanol-hydrogen peroxide solution (30%, 10 cm^3) and stirred for 2 hours The mixture was extracted with dichloromethane (3 × 50 cm^3), washed with saturated aqueous sodium hydrogen carbonate solution (10 cm^3), brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. The relative and absolute stereochemistry was assumed as drawn from literature precedent and from the small α-proton coupling constant (5.0 Hz). The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (CH_2Cl_2) gave **223** as a yellow oil in 63% yield; R_f (CH_2Cl_2) = 0.18; $[\alpha]_D^{25}$ = +19 (c = 0.48, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.33-7.19 (5H, m, Ph), 5.88 (1H, ddd, J = 17.0 Hz, 10.5 Hz and 5.5 Hz, C*H*=$H_{cis}H_{trans}$), 5.73 (1H, d, J = 5.0 Hz, ClCH), 5.42 (1H, app. dt, J = 17.0 Hz and 1.5 Hz, CH=$H_{cis}H_{trans}$), 5.30 (1H, app. dt, J = 10.0 Hz and 1.0 Hz, CH=$H_{cis}H_{trans}$), 4.66 (1H, m, C*H*OH), 4.49 (1H, dd, J = 9.5 Hz and 4.0 Hz, CHN), 3.15 (1H, dd, J = 14.5 Hz and 4.0 Hz, PhCH_AH_B), 2.90 (1H, dd, J = 14.5 Hz and 9.5 Hz, PhCH_AH_B), 2.82 (1H, broad s, OH), 1.38 (3H, s, (CH_3)C(CH_3)), 1.35 (3H, s, (CH_3)C(CH_3)); δC (75MHz, $CDCl_3$) 168.3, 152.4, 136.7, 135.3, 129.5, 129.2, 127.4,

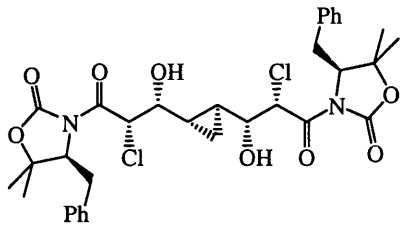
119.3, 83.6, 73.3, 64.4, 59.5, 35.3, 28.9, 22.6; IR (Film / cm^{-1}) 3473 (broad OH), 1777 ($C=O_{ox}$), 1706 (C=O); HRMS : m/z (ES) $[M+H]^+$ requires 338.1154, found 338.1154.

3.14.3(*E*)-(2*S*,3*R*,6*R*,7*S*)-1,8-*Bis*-((*S*)-4-benzyl-5,5-dimethyl-2-oxo-oxazolidin-3-yl)-2,7-dichloro-3,6-dihydroxy-oct-4-ene-1,8-dione 224



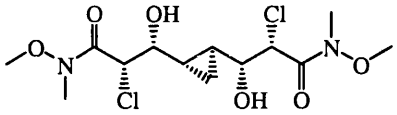
To a solution of (*S*)-4-Benzyl-3-((2*S*,3*R*)-2-chloro-3-hydroxy-pent-4-enoyl)-5,5-dimethyl-oxazolidin-2-one **223** (1 equivalent) in dry degassed dichloromethane (10 cm^3) under nitrogen was added 2nd generation Grubbs' catalyst (2 mol%) and the solution refluxed for 5 hours. The reaction was allowed to cool to room temperature and the solution was pushed through a plug of silica (2 cm^3), with ether as eluent (10 cm^3). The solvent was removed under reduced pressure to give the crude product. The relative and absolute stereochemistry was assumed as drawn from literature. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (Et_2O:Hexane, 60:40) gave **224** as a yellow oil in 91% yield; R_f (CH_2Cl_2) = 0.10; $[\alpha]_D^{25}$ = -10 (c = 1.15, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.28-7.13 (10H, m, 2 x Ph), 5.92 (2H, d, J = 2.5 Hz, 2 x CHCl), 5.64 (2H, d, J = 4.0 Hz, CH=CH), 4.64 (2H, m, 2 x C*H*OH), 4.47 (2H, dd, J = 10.0 Hz and 4.0 Hz, 2 x CHN), 3.12 (2H, dd, J = 14.5 Hz and 4.0 Hz, 2 x PhCH_AH_B), 2.89 (2H, broad s, 2 x OH), 2.84 (2H, dd, J = 14.5 Hz and 10.0 Hz, 2 x PhCH_AH_B), 1.33, (6H, s, 2 x (CH_3)C(CH_3)), 1.32 (6H, s, 2 x (CH_3)C(CH_3)); δC (75MHz, $CDCl_3$) 168.2, 152.4, 136.8, 131.1, 129.5, 129.2, 127.4, 83.7, 71.8, 64.4, 59.3, 35.1, 28.9, 22.7; IR (Film / cm^{-1}) 3481 (broad OH), 1773 ($C=O_{ox}$), 1700 (C=O); HRMS: m/z (ES) $[M+NH_4]^+$ requires 664.2187, found 664.2194.

3.14.4(2*S*,3*R*,4*R*,5*R*,6*R*,7*S*)-1,8-*Bis*-((*S*)-4-benzyl-5,5-dimethyl-2-oxo-oxazolidin-3-yl)-2,7-dichloro-3,6-dihydroxy-4,5-cyclopropyl-oct-1,8-dione 225



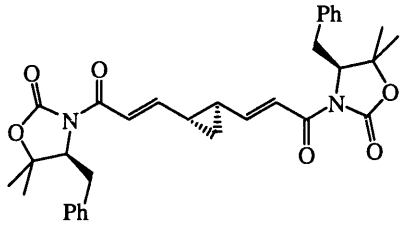
Diethyl zinc (5 equivalents, 1.0 mol dm^{-3} solution in hexane) was added in one portion *via* syringe to a stirred solution of **224** (1 equivalent) in dry dichloromethane at -40°C, before the immediate addition of diiodomethane (5 equivalents) in one portion *via* syringe, under nitrogen and in the absence of light. The solution was allowed to warm to 0°C over 6 hours. The reaction was maintained at this temperature for 12 hours before being quenched with saturated sodium sulfite solution (5 cm^3) and stirred for 10 minutes. Hydrochloric acid (1.0 mol dm^{-3} solution in water), sufficient to dissolve the white precipitate, was added and the mixture was extracted with dichloromethane (3 x 10 cm^3), washed with brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. The all-*syn* stereochemistry was assigned as drawn due to literature precedent in the minimisation the $A^{1,3}$-strain in the transition state. The diastereomeric excess was determined as 81% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (Et_2O:Hexane, 60:40) gave **225** as a yellow oil in 55% yield; R_f (CH_2Cl_2) = 0.10; $[\alpha]_D^{25}$ = +38 (c = 0.60, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 7.31-7.16 (10H, m, 2 x Ph), 5.82 (2H, d, J = 3.5 Hz, 2 x CHCl), 4.51 (2H, dd, J = 10.0 Hz and 3.5 Hz, 2 x CHN), 3.62 (2H, m, 2 x C*H*OH), 3.21 (2H, dd, J = 14.5 Hz and 3.5 Hz, 2 x PhCH_AH_B), 2.86 (2H, dd, J = 14.5 Hz and 10.0 Hz, 2 x PhCH_AH_B), 2.84 (2H, broad s, 2 x OH), 1.36 (6H, s, 2 x (CH_3)C(CH_3)), 1.33 (6H, s, 2 x (CH_3)C(CH_3)), 1.32 (2H, obs. m, cyclopropyl-CH), 0.85 (2H, app. t, J = 7.0 Hz, cyclopropyl-CH_2); δC (75MHz, $CDCl_3$) 168.5, 152.4, 136.9, 129.4, 129.2, 127.4, 83.7, 74.0, 64.6, 61.1, 35.0, 29.0, 22.8 19.3, 9.6; IR (Film / cm^{-1}) 3480 (broad O-H), 1772 (C=O_{ox}), 1713 (C=O); HRMS: m/z (ES) $[M+Na]^+$ requires 683.1897, found 683.1901.

3.14.5(2*S*,3*R*)-2-Chloro-3-{(1*S*,2*S*)-2-[(1*R*,2*S*)-2-chloro-1-hydroxy-2-(methoxy-methyl-carbamoyl)-ethyl]-cyclopropyl}-3-hydroxy-*N*-methoxy-*N*-methyl-propionamide 232



$AlMe_3$ (4 equivalents, 1 mol dm^{-3} solution in toluene) was added dropwise to a suspension of MeNHOMe (4 equivalents) in dry THF at 0°C under nitrogen and stirred for thirty minutes, until a homogeneous solution formed. (2*S*,3*R*,4*R*,5*R*,6*R*,7*S*)-1,8-*bis*-((*S*)-4-benzyl-5,5-dimethyl-2-oxo-oxazolidin-3-yl)-2,7-dichloro-3,6-dihydroxy-4,5-cyclopropyl-oct-1,8-dione **225** (1 equivalent) as a solution in dry THF was then added dropwise, the solution allowed to warm to room temperature and stirred for 12 hours. The reaction was cautiously quenched with saturated aqueous tartaric acid (2 cm^3), extracted with dichloromethane (3 x 20 cm^3), washed with brine (10 cm^3) and dried. The solvent was removed under reduced pressure to give the crude product. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (EtOAc:Hexane, 80:20) gave **232** as a yellow oil in 55% yield; R_f (EtOAc:Hexane, 80:20) = 0.15; $[\alpha]_D^{25}$ = -2 (c = 1.08, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 5.13 (2H, broad s, OH), 4.73 (2H, d, J = 1.5 Hz, CHCl), 3.38 (2H, dd, J = 8.3 Hz and 1.5 Hz, C*H*OH), 3.15 (6H, s, CH_3O), 2.99 (6H, s, CH_3N), 1.08 (2H, m, cyclopropyl-CH), 0.97 (2H, m, cyclopropyl-CH_2); δC (75MHz, $CDCl_3$) 169.9, 75.5, 56.6, 38.0, 36.3, 18.4, 13.1; IR (Film / cm^{-1}) 3401 (broad OH), 1640 (C=O); HRMS: no molecular ion found.

3.14.6(2*E*,4*R*,5*R*,7*E*)-1,8-*Bis*-((*S*)-4-benzyl-5,5-dimethyl-2-oxo-oxazolidin-3-yl)-2,7-ene-4,5-cyclopropyl-oct-1,8-dione 226



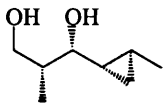
Samarium(II) iodide (2.5 equivalents, 0.1 mol dm^{-3} solution in THF) was added dropwise to solution of (2*S*,3*R*,4*R*,5*R*,6*R*,7*S*)-1,8-*Bis*-((*S*)-4-benzyl-5,5-dimethyl-2-oxo-oxazolidin-3-yl)-2,7-dichloro-3,6-dihydroxy-4,5-cyclopropyl-oct-1,8-dione **225** (1 equivalent) in dry degassed THF (10 cm^3) at room temperature under nitrogen and stirred for two hours. The reaction was then quenched with hydrochloric acid (5 cm^3, 1 mol dm^3 solution in water), washed with sodium thiosulphate (5 cm^3, saturated solution in water), extracted with ethyl acetate (3 x 10 cm^3), washed with brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give crude product. The diastereomeric excess was determined to be >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification by recrystallisation (EtOAc/Hexane) gave **226** as a white solid in 37% yield; R_f (EtOAc:Hexane, 20:80) = 0.56; $[\alpha]_D^{25}$ = +193 (c = 0.28, CH_2Cl_2); mp (EtOAc/Hexane) = 193-196°C; δH (300 MHz, $CDCl_3$) 7.35 (2H, d, J = 15.0 Hz, 2 x COC*H*=CH), 7.31-7.17 (10H, m, 2 x Ph), 6.59 (2H, dd, J = 15.0 Hz and 9.5 Hz, 2 x COCH=C*H*), 4.52 (2H, dd, J = 10.0 Hz and 4.0 Hz, 2 x CHN), 3.18 (2H, dd, J = 14.5 Hz and 4.0 Hz, 2 x CH_AH$_B$Ph), 2.86 (2H, dd, J = 14.5 Hz and 10.0 Hz, 2 x CH$_A$$H_B$Ph), 1.97 (2H, app. q, J = 8.0 Hz, 2 x cyclopropyl-CH), 1.39-1.27 (2H, obs. m, cyclopropyl-CH_2), 1.35 (6H, s, 2 x (CH_3)C(CH$_3$)), 1.33 (6H, s, 2 x (CH$_3$)C(CH_3)); δC (75MHz, $CDCl_3$) 165.2, 153.0, 151.9, 137.5, 129.5, 129.1, 127.2, 119.8, 82.6, 64.2, 35.7, 29.0, 26.9, 22.7, 18.8; IR (KBr / cm^{-1}) 1760 (C=O$_{ox}$), 1684 (C=O); HRMS: m/z (ES) $[M+H]^+$ requires 557.2646, found 557.2649.

3.14.7(*E*)-3-[(1*R*,2*R*)-2-((*E*)-3-Hydroxy-propenyl)-cyclopropyl]-propenol 241

226 was dissolved in CH_2Cl_2 (2 cm^3) at -78°C under nitrogen and DIBAL-H (4 equivalents) was added in one portion. The reaction was stirred for 2 hours before being quenched with saturated aqueous ammonium chloride solution (5 cm^3) at -78°C, before allowing the reaction to warm to room temperature over 2 hours. The crude mixture was washed with saturated aqueous hydrogen carbonate solution (5 cm^3), extracted with CH_2Cl_2 (3 x 5 cm^3) and dried $MgSO_4$; the solvent was removed under reduced pressure to give the crude product, which was not further isolated. The crude reaction mixture was then further reduced by the addition of sodium borohydride (2.5 equivalents) in THF (5 cm^3) at room for 1 hour. The reaction was then quenched with saturated aqueous sodium hydrogen carbonate solution (5 cm^3), extracted with ethyl acetate (3 x 5 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. Purification by silica gel chromatography gave **241** in 39% overall yield which matched the previously published data for this compound[169]; R_f (EtOAc:Hexane, 80:20) = 0.32; $[\alpha]_D^{25}$ = -105 (c = 0.10, EtOH); δH (300 MHz, $CDCl_3$) 5.71 (2H, dt, J = 15.0 Hz and 6.0 Hz, 2 x C*H*=CH-cyclopropane), 5.32 (2H, dd, J = 15.0 Hz and 8.5 Hz, 2 x CH=C*H*-cyclopropane), 4.09 (4H, app. d, J = 6.5 Hz, 2 x CH_2OH), 1.65-1.40 (2H, m, 2 x cyclopropyl-CH), 0.87 (2H, app. t, J = 7.0 Hz, cyclopropyl-CH_2).

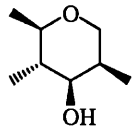
Chapter 3.15 General procedures for the electrophilic ring opening of cyclopropanes

3.15.1(1*R*,2*R*)-2-methyl-1-((1*S*,2*S*)-2-methylcyclopropyl)propane-1,3-diol 249



$LiAlH_4$ (2.2 equivalents, 1 mol dm^{-3} solution in THF) was added dropwise to a solution of **147g** (1 equivalent) in dry THF (10 cm^3) at 0°C under nitrogen. The reaction was stirred for 1 hour, and then quenched with sodium hydroxide solution (1 cm^3, 5 mol dm^{-3} solution in water), filtered through Celite with ethyl acetate as eluent (10 cm^3), and then extracted with ethyl acetate (3 x 10 cm^3). The crude reaction mixture was washed with brine (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, EtOAc:hexane, 50:50) gave **249** as a yellow oil in 92% yield; R_f (EtOAc:Hexane; 50:50) = 0.34; $[\alpha]_D^{25}$ = +32 (c = 0.34, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 3.76 (1H, dd, J = 10.5 Hz and 7.0 Hz, CH_AH_BOH), 3.64 (1H, dd, J = 10.5 Hz and 6.0 Hz, CH_AH_BOH), 2.5 (2H, broad s, 2 x OH), 1.99 (1H, m, $CHCH_2OH$), 1.03 (3H, d, J = 6.0 Hz, CH_3-cylopropane), 0.98 (3H, d, J = 7.0 Hz, CH_3), 0.71 (1H, m, cyclopropyl-C*H*-CHOH), 0.61 (1H, m, cyclopropyl-C*H*-CH_3), 0.46 (1H, app. dt, J = 8.5 Hz and 4.5 Hz, cyclopropyl-CH_AH_B), 0.30 (1H, app. dt, J = 8.0 Hz and 5.0 Hz, cyclopropyl-CH_AH_B); δC (75MHz, $CDCl_3$) 78.5, 75.6, 65.6, 38.8, 17.2, 10.6, 10.3, 10.0; IR (film / cm^{-1}) 3368 (broad O-H); HRMS: m/z (ES) $[M+NH_4]^+$ requires 162.1489, found 162.1491.

3.15.2(2*R*,3*S*,4*R*,5*R*)-tetrahydro-2,3,5-trimethyl-2H-pyran-4-ol 251

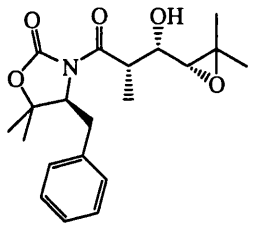


Mercury trifluoroacetate (2.5 equivalents) was added in one portion to a solution of (1*R*,2*R*)-2-methyl-1-((1*S*,2*S*)-2-methylcyclopropyl)propane-1,3-diol **249** (1 equivalent) in dry dichloromethane under nitrogen at room temperature and stirred for 24 hours. Saturated aqueous sodium chloride solution was then added (2 cm^3) and the solution was stirred for 1 hour. The mixture was extracted with dichloromethane (3 x 10 cm^3), washed with saturated aqueous sodium hydrogen carbonate solution (10 cm^3). The solvent removed under reduced pressure to give the crude organomercury product, which was carried onto the next step without further purification.

AIBN (2 mol%) was added to a solution of the crude organomercury product in dry THF under nitrogen at room temperature. Bu_3SnH (4 equivalents) was then added in one portion and stirred for 2 hours, which lead to the precipitation of mercury. The reaction was quenched with saturated aqueous sodium fluoride solution (2 cm^3), diluted with EtOAc (10 cm^3) and filtered through Celite. The solution was dried ($MgSO_4$) and the solvent removed under reduced to give the crude product. The diastereomeric excess was determined as >95% by examination of the crude 300 MHz ^{1}H-NMR spectrum. Purification *via* column chromatography (SiO_2, EtOAc:Hexane, 30:70) gave **251** as a yellow oil in 91% yield; R_f (CH_2Cl_2) = 0.18; $[\alpha]_D^{25}$ = -3 (c = 0.67, CH_2Cl_2); δH (300 MHz, $CDCl_3$) 3.81 (1H, dd, J = 11.5 Hz and 5.0 Hz, OC*H*$_A$H$_B$), 3.13- 3.01 (2H, app. t and obs. m, J = 11.5 Hz, OCH$_A$*H*$_B$ and OC*H*CH_3), 2.83 (1H, app. t, J = 10.0 Hz, C*H*OH), 1.78 (1H, broad s, OH), 1.64 (1H, m, C*H*CH_2), 1.24 (1H, obs. m, C*H*CH_3), 1.20 (3H, d, J = 6.5 Hz, C*H*$_3$CHO), 0.96 (3H, d, J = 6.5 Hz, CH_3), 0.90 (3H, d, J = 6.5 Hz, CH_3); δC (75MHz, $CDCl_3$) 79.3, 78.6, 72.3, 45.9, 39.6, 20.0, 13.8, 13.7; IR (film / cm^{-1}) 3400 (broad O-H); HRMS: no molecular ion found

Chapter 3.16 General procedure for the hydroxyl-directed epoxidation of *syn*-aldols

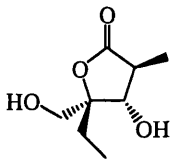
3.16.1 (*S*)-4-Benzyl-3-[(2*S*,3*S*)-3-((*R*)-3,3-dimethyl-oxiranyl)-3-hydroxy-2-methyl-propionyl]-5,5-dimethyl-oxazolidin-2-one 261



$VO(acac)_2$ (10 mol%) was added in one portion to a solution of **147h** in dry benzene (5 cm^3) under nitrogen, at room temperature and stirred for 5 minutes. *tert*-Butyl hydrogen peroxide (1.1 equivalents, 5-6 mol dm^{-3} solution in decane) was then *via* syringe in one portion and the reaction stirred for 2 hours. The solvent was then removed under reduced pressure and the residue was dissolved in dichloromethane (10 cm^3), washed with distilled water (10 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product in a non-optimised 72% de, as determined by examination of the crude 300 MHz ^{1}H-NMR spectrum. The relative and absolute stereochemistry was assumed as drawn from literature precedent and minimisation $A^{1,3}$-strain in the transition state. Purification by recrystallisation (Et_2O, Hexane) gave **261** in 73% yield and in >95% de. R_f (CH_2Cl_2) = 0.25; $[\alpha]_D^{25}$ = -10 (c = 0.48, CH_2Cl_2); mp = decomposed >50°C; δH (300 MHz, Benzene-d^6) 7.23-6.96 (5H, m, Ph), 4.41 (1H, dd, J = 7.0 Hz and 5.5 Hz, C*H*OH), 4.33 (1H, dd, J = 9.5 Hz and 4.0 Hz, CHN), 3.80 (1H, m, C*H*CH_3), 3.00 (1H, d, J = 7.0 Hz, epoxide-CH), 2.88 (1H, dd, J = 14.5 Hz and 4.0 Hz, C$H_A$$H_B$Ph), 2.37 (1H, obs. dd, J = 14.5 Hz and 9.5 Hz, C$H_A$$H_B$Ph), 2.36 (1H, obs. d, J = 4.0 Hz, OH), 1.25 (1H, d, J = 7.0 Hz,

CH_3CH), 1.17 (3H, s, $(CH_3)C(CH_3)$), 1.03 (3H, s, $(CH_3)C(CH_3)$), 0.86 (3H, s, epoxide-CH_3), 0.85 (3H, s, epoxide-CH_3); δC (75MHz, Benzene-d^6) 175.3, 152.9, 137.9, 129.8, 129.2, 127.3, 82.1, 71.4, 65.5, 64.1, 59.6, 42.1, 35.7, 28.2, 25.2, 22.2, 19.9, 12.9; IR (KBr / cm^{-1}) 3466 (broad O-H), 1776 ($C=O_{ox}$), 1693 (C=O); HRMS: no molecular ion found.

3.16.2(3*S*,4*S*,5*S*)-5-ethyl-dihydro-4-hydroxy-5-(hydroxymethyl)-3-methylfuran-2(3H)-one 256

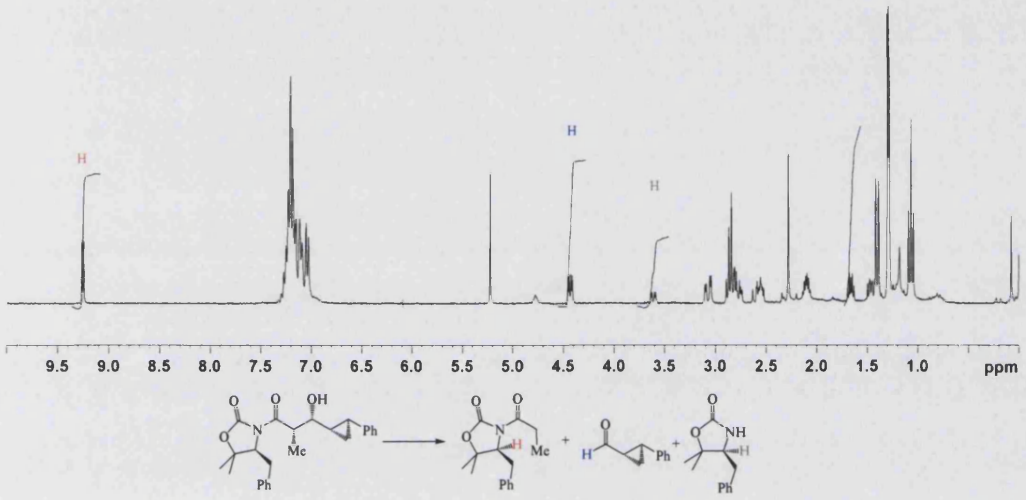


$VO(acac)_2$ (10 mol%) was added in one portion to a solution of **255** in dry benzene (5 cm^3) under nitrogen, at room temperature and stirred for 5 minutes. *tert*-Butyl hydrogen peroxide (1.1 equivalents, 5-6 mol dm^{-3} solution in decane) was then added *via* syringe in one portion and the reaction stirred for 2 hours. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (10 ml), washed with distilled water (10 cm^3) and dried ($MgSO_4$). The organic solvent was removed under reduced pressure to give (*S*)-4-Benzyloxazolidin-2-one **126** in 78% yield, which matched the previously described data for this compound. The aqueous solvent was saturated with sodium chloride, extracted with ethyl acetate (3 x 20 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product in a non-optimised 81% de. The relative and absolute stereochemistry was assumed as drawn from literature precedent and minimisation $A^{1,3}$-strain in the transition state. Purification by recrystallisation (EtOAc, Hexane) gave **258** in 71% yield and in >95% de. R_f (CH_2Cl_2) = 0.12; $[\alpha]_D^{25}$ = -19 (c = 0.16, CH_2Cl_2); mp = 76-77°C; δH (300 MHz, D_2O) 3.91 (1H, d, J = 9.5 Hz, C*H*OH), 3.71 (1H, d, J = 13.0 Hz, CH_AH_BOH), 3.52 (1H, d, J = 13.0 Hz, CH_AH_BOH), 2.77 (1H, dq, J = 10.0 Hz and 7.0 Hz, C*H*CH_3), 1.59-1.47 (2H, app. qd, J = 7.0 Hz and 2.5 Hz, CH_2CH_3), 1.03 (3H, d, J = 7.0 Hz, CH_3CH), 0.72 (3H, t, J = 7.5 Hz, CH_3CH_2); δC

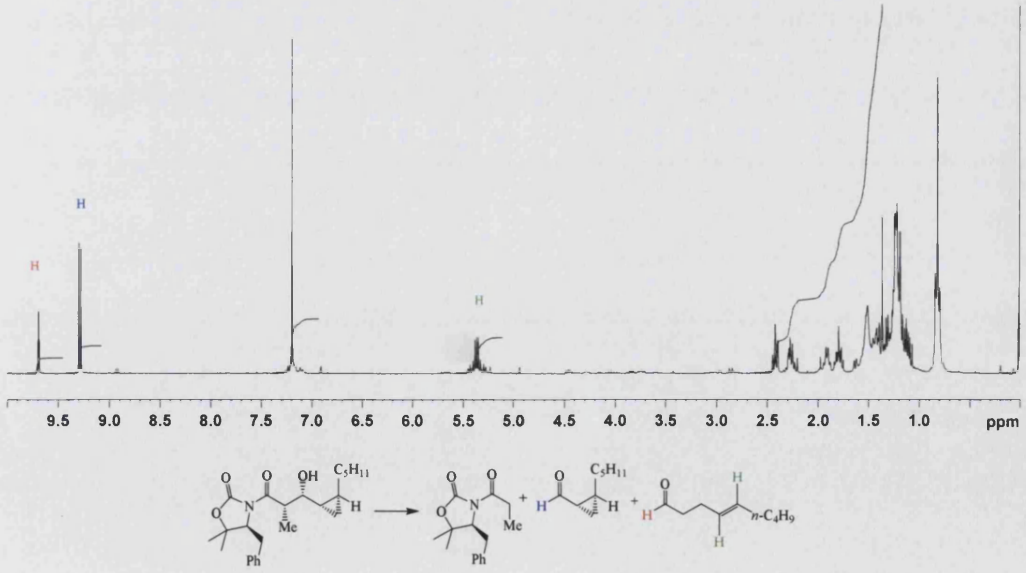
(75MHz, D_2O) 181.0, 89.7, 77.9, 62.5, 43.3, 27.4, 12.8, 6.9; IR (KBr / cm^{-1}) 3348 (broad O-H), 1751 (C=O); HRMS: m/z (ES) $[M+NH_4]^+$ requires 192.1230, found 192.1233.

4 Appendices

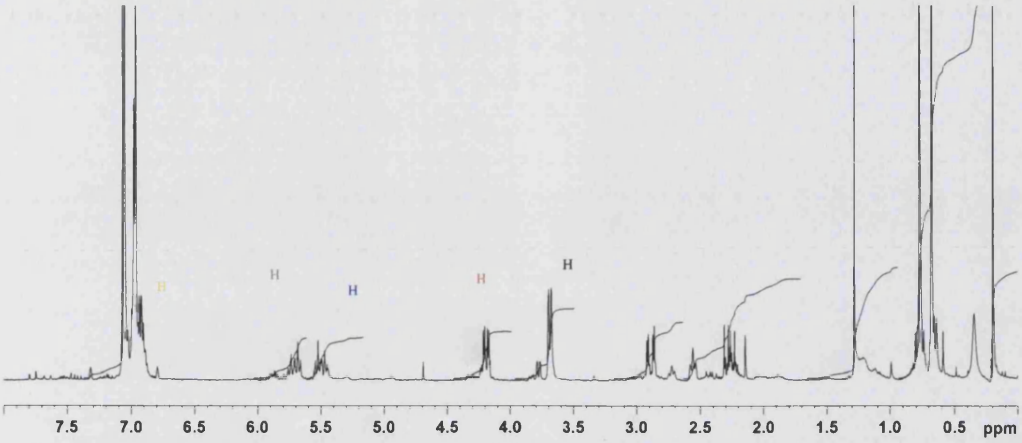
Appendix 4.1

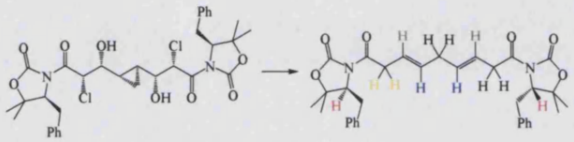


Appendix 4.2

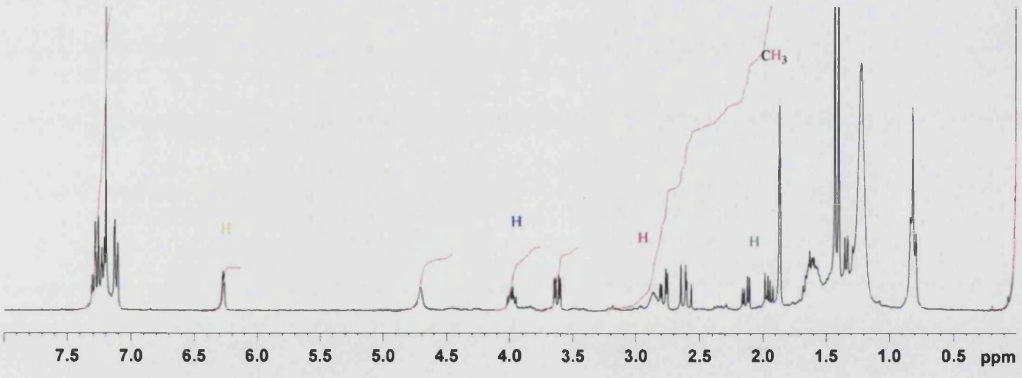


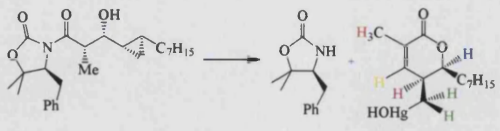
Appendix 4.3





Appendix 4.4





Appendix 4.5

Crystal Structure Data

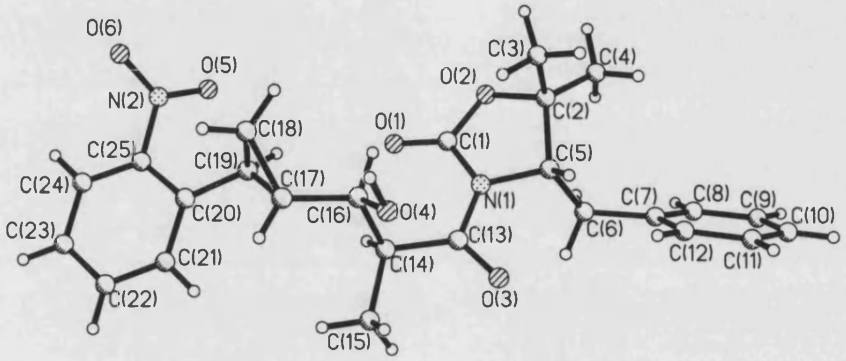


Table 1. Crystal data and structure refinement for **147d**.

Identification code	h04sdb01
Empirical formula	C25 H28 N2 O6
Formula weight	174.19
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P 2_1 2_1 2_1
Unit cell dimensions	a = 7.67000(10) Å α= 90°. b = 14.8370(3) Å β= 90° c = 20.5190(3) Å γ = 90°.
Volume	2335.06(7) $Å^3$
Z	4
Density (calculated)	1.287 Mg/m^3
Absorption coefficient	0.092 mm^{-1}
F(000)	960
Crystal size	0.15 x 0.13 x 0.08 mm^3
Theta range for data collection	3.59 to 27.46°.
Index ranges	-6<=h<=7; -18<=k<=18; -7<=l<=7
Reflections collected	43530
Independent reflections	5310 [R(int) = 0.1280]
Completeness to theta = 27.46°	99.2 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2

Data / restraints / parameters	5310 / 0 / 303
Goodness-of-fit on F^2	1.029
Final R indices [I>2sigma(I)])]	R1 = 0.0382, wR2 = 0.0792
R indices (all data)	R1 = 0.0568, wR2 = 0.0862
Absolute structure parameter	0.6(7)
Extinction coefficient	0.033(3)
Largest diff. peak and hole	0.242 and -0.263 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **152b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(3)	2664(1)	3554(1)	787(1)	30(1)
O(1)	7197(2)	3212(1)	1909(1)	37(1)
O(5)	10441(2)	1007(1)	2374(1)	39(1)
O(2)	7620(2)	4631(1)	1568(1)	36(1)
O(6)	11954(2)	-118(1)	2004(1)	43(1)
O(4)	5197(1)	2138(1)	65(1)	31(1)
N(2)	10569(2)	237(1)	2165(1)	31(1)
C(15)	2771(2)	1741(1)	1094(1)	29(1)
C(20)	7548(2)	40(1)	1771(1)	26(1)
C(1)	6725(2)	3856(1)	1599(1)	32(1)
C(16)	5874(2)	2034(1)	707(1)	26(1)
N(1)	5224(2)	3947(1)	1221(1)	28(1)
C(19)	7640(2)	921(1)	1418(1)	26(1)
C(18)	8434(2)	905(1)	740(1)	30(1)
C(23)	7549(2)	-1692(1)	2345(1)	34(1)
C(13)	3988(2)	3294(1)	1055(1)	26(1)
C(17)	6515(2)	1084(1)	827(1)	26(1)
C(24)	9019(2)	-1160(1)	2386(1)	31(1)
C(7)	2817(2)	6191(1)	1127(1)	31(1)
C(6)	3607(2)	5363(1)	1436(1)	32(1)
C(5)	4984(2)	4889(1)	1014(1)	29(1)
C(21)	6088(2)	-519(1)	1749(1)	33(1)
C(14)	4407(2)	2315(1)	1179(1)	25(1)
C(4)	7160(2)	6182(1)	1277(1)	39(1)
C(12)	2188(2)	6172(1)	491(1)	38(1)
C(3)	7868(2)	5008(1)	433(1)	43(1)
C(22)	6088(2)	-1365(1)	2033(1)	38(1)
C(2)	6885(2)	5220(1)	1055(1)	32(1)
C(25)	8976(2)	-312(1)	2109(1)	26(1)
C(8)	2604(2)	6980(1)	1483(1)	41(1)
C(10)	1190(3)	7699(1)	577(1)	57(1)
C(11)	1372(2)	6918(1)	216(1)	50(1)
C(9)	1805(3)	7732(1)	1209(1)	53(1)

Table 3. Bond lengths [Å] and angles [°] for **147d**.

O(3)-C(13)	1.2175(18)	C(17)-H(17)	1.0000
O(1)-C(1)	1.2036(19)	C(24)-C(25)	1.380(2)
O(5)-N(2)	1.2246(18)	C(24)-H(24)	0.9500
O(2)-C(1)	1.3409(19)	C(7)-C(8)	1.390(2)
O(2)-C(2)	1.4801(19)	C(7)-C(12)	1.391(2)
O(6)-N(2)	1.2312(18)	C(6)-C(5)	1.535(2)
O(4)-H(1)	0.9785	C(6)-H(6A)	0.9900
N(2)-C(25)	1.473(2)	C(6)-H(6B)	0.9900
C(15)-C(14)	1.526(2)	C(5)-C(2)	1.541(2)
C(15)-H(15A)	0.9800	C(5)-H(5)	1.0000
C(15)-H(15B)	0.9800	C(21)-C(22)	1.384(2)
C(15)-H(15C)	0.9800	C(21)-H(21)	0.9500
C(20)-C(21)	1.393(2)	C(14)-H(14)	1.0000
C(20)-C(25)	1.398(2)	C(4)-C(2)	1.513(2)
C(20)-C(19)	1.496(2)	C(4)-H(4A)	0.9800
C(1)-N(1)	1.395(2)	C(4)-H(4B)	0.9800
C(16)-C(17)	1.513(2)	C(4)-H(4C)	0.9800
C(16)-C(14)	1.542(2)	C(12)-C(11)	1.391(2)
C(16)-H(16)	1.0000	C(12)-H(12)	0.9500
N(1)-C(13)	1.3977(19)	C(3)-C(2)	1.515(2)
N(1)-C(5)	1.4718(19)	C(3)-H(3A)	0.9800
C(19)-C(17)	1.509(2)	C(3)-H(3B)	0.9800
C(19)-C(18)	1.519(2)	C(3)-H(3C)	0.9800
C(19)-H(19)	1.0000	C(22)-H(22)	0.9500
C(18)-C(17)	1.506(2)	C(8)-C(9)	1.392(3)
C(18)-H(18A)	0.9900	C(8)-H(8)	0.9500
C(18)-H(18B)	0.9900	C(10)-C(9)	1.380(3)
C(23)-C(24)	1.378(2)	C(10)-C(11)	1.383(3)
C(23)-C(22)	1.379(2)	C(10)-H(10)	0.9500
C(23)-H(23)	0.9500	C(11)-H(11)	0.9500
C(13)-C(14)	1.509(2)	C(9)-H(9)	0.9500

C(1)-O(2)-C(2)	110.19(12)	O(1)-C(1)-N(1)	128.27(14)
C(16)-O(4)-H(1)	110.9	O(2)-C(1)-N(1)	108.24(12)
O(5)-N(2)-O(6)	124.24(14)	O(4)-C(16)-C(17)	111.67(12)
O(5)-N(2)-C(25)	118.52(13)	O(4)-C(16)-C(14)	106.59(12)
O(6)-N(2)-C(25)	117.23(13)	C(17)-C(16)-C(14)	112.76(12)
C(14)-C(15)-H(15A)	109.5	O(4)-C(16)-H(16)	108.6
C(14)-C(15)-H(15B)	109.5	C(17)-C(16)-H(16)	108.6
H(15A)-C(15)-H(15B)	109.5	C(14)-C(16)-H(16)	108.6
C(14)-C(15)-H(15C)	109.5	C(1)-N(1)-C(13)	128.90(12)
H(15A)-C(15)-H(15C)	109.5	C(1)-N(1)-C(5)	110.82(12)
H(15B)-C(15)-H(15C)	109.5	C(13)-N(1)-C(5)	120.23(12)
C(21)-C(20)-C(25)	115.07(13)	C(20)-C(19)-C(17)	120.12(13)
C(21)-C(20)-C(19)	122.82(13)	C(20)-C(19)-C(18)	116.61(12)
C(25)-C(20)-C(19)	121.96(14)	C(17)-C(19)-C(18)	59.66(10)
O(1)-C(1)-O(2)	123.48(14)	C(20)-C(19)-H(19)	116.2

C(17)-C(19)-H(19)	116.2	C(15)-C(14)-C(16)	112.22(12)
C(18)-C(19)-H(19)	116.2	C(13)-C(14)-H(14)	108.8
C(17)-C(18)-C(19)	59.82(10)	C(15)-C(14)-H(14)	108.8
C(17)-C(18)-H(18A)	117.8	C(16)-C(14)-H(14)	108.8
C(19)-C(18)-H(18A)	117.8	C(2)-C(4)-H(4A)	109.5
C(17)-C(18)-H(18B)	117.8	C(2)-C(4)-H(4B)	109.5
C(19)-C(18)-H(18B)	117.8	H(4A)-C(4)-H(4B)	109.5
H(18A)-C(18)-H(18B)	114.9	C(2)-C(4)-H(4C)	109.5
C(24)-C(23)-C(22)	119.44(14)	H(4A)-C(4)-H(4C)	109.5
C(24)-C(23)-H(23)	120.3	H(4B)-C(4)-H(4C)	109.5
C(22)-C(23)-H(23)	120.3	C(11)-C(12)-C(7)	121.33(17)
O(3)-C(13)-N(1)	117.07(13)	C(11)-C(12)-H(12)	119.3
O(3)-C(13)-C(14)	124.00(13)	C(7)-C(12)-H(12)	119.3
N(1)-C(13)-C(14)	118.82(12)	C(2)-C(3)-H(3A)	109.5
C(18)-C(17)-C(19)	60.52(10)	C(2)-C(3)-H(3B)	109.5
C(18)-C(17)-C(16)	117.55(13)	H(3A)-C(3)-H(3B)	109.5
C(19)-C(17)-C(16)	117.75(13)	C(2)-C(3)-H(3C)	109.5
C(18)-C(17)-H(17)	116.5	H(3A)-C(3)-H(3C)	109.5
C(19)-C(17)-H(17)	116.5	H(3B)-C(3)-H(3C)	109.5
C(16)-C(17)-H(17)	116.5	C(23)-C(22)-C(21)	120.92(15)
C(23)-C(24)-C(25)	118.53(14)	C(23)-C(22)-H(22)	119.5
C(23)-C(24)-H(24)	120.7	C(21)-C(22)-H(22)	119.5
C(25)-C(24)-H(24)	120.7	O(2)-C(2)-C(4)	106.86(13)
C(8)-C(7)-C(12)	118.04(15)	O(2)-C(2)-C(3)	106.67(13)
C(8)-C(7)-C(6)	120.71(15)	C(4)-C(2)-C(3)	112.33(14)
C(12)-C(7)-C(6)	121.14(14)	O(2)-C(2)-C(5)	102.13(12)
C(7)-C(6)-C(5)	114.31(13)	C(4)-C(2)-C(5)	116.67(14)
C(7)-C(6)-H(6A)	108.7	C(3)-C(2)-C(5)	111.08(13)
C(5)-C(6)-H(6A)	108.7	C(24)-C(25)-C(20)	124.25(14)
C(7)-C(6)-H(6B)	108.7	C(24)-C(25)-N(2)	116.89(13)
C(5)-C(6)-H(6B)	108.7	C(20)-C(25)-N(2)	118.84(13)
H(6A)-C(6)-H(6B)	107.6	C(7)-C(8)-C(9)	120.87(19)
N(1)-C(5)-C(6)	111.02(13)	C(7)-C(8)-H(8)	119.6
N(1)-C(5)-C(2)	99.73(12)	C(9)-C(8)-H(8)	119.6
C(6)-C(5)-C(2)	118.32(13)	C(9)-C(10)-C(11)	119.85(18)
N(1)-C(5)-H(5)	109.1	C(9)-C(10)-H(10)	120.1
C(6)-C(5)-H(5)	109.1	C(11)-C(10)-H(10)	120.1
C(2)-C(5)-H(5)	109.1	C(10)-C(11)-C(12)	119.7(2)
C(22)-C(21)-C(20)	121.73(14)	C(10)-C(11)-H(11)	120.1
C(22)-C(21)-H(21)	119.1	C(12)-C(11)-H(11)	120.1
C(20)-C(21)-H(21)	119.1	C(10)-C(9)-C(8)	120.18(18)
C(13)-C(14)-C(15)	110.03(12)	C(10)-C(9)-H(9)	119.9
C(13)-C(14)-C(16)	108.04(12)	C(8)-C(9)-H(9)	119.9

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for h04sdb01. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}$

Atom	U11	U22	U33	U23	U13	U12
O(3)	29(1)	30(1)	32(1)	-1(1)	-6(1)	2(1)
O(1)	40(1)	30(1)	42(1)	3(1)	-16(1)	0(1)
O(5)	44(1)	34(1)	39(1)	-1(1)	-10(1)	-6(1)
O(2)	36(1)	30(1)	44(1)	3(1)	-13(1)	-6(1)
O(6)	25(1)	48(1)	56(1)	16(1)	3(1)	4(1)
O(4)	30(1)	38(1)	25(1)	5(1)	3(1)	8(1)
N(2)	27(1)	37(1)	28(1)	9(1)	-4(1)	-2(1)
C(15)	27(1)	27(1)	34(1)	1(1)	4(1)	-2(1)
C(20)	25(1)	28(1)	25(1)	-1(1)	2(1)	3(1)
C(1)	32(1)	29(1)	35(1)	-2(1)	-7(1)	-2(1)
C(16)	24(1)	26(1)	28(1)	4(1)	-1(1)	-1(1)
N(1)	30(1)	22(1)	31(1)	0(1)	-7(1)	0(1)
C(19)	23(1)	27(1)	27(1)	0(1)	-1(1)	-1(1)
C(18)	27(1)	32(1)	31(1)	5(1)	2(1)	2(1)
C(23)	37(1)	28(1)	36(1)	9(1)	1(1)	-3(1)
C(13)	27(1)	29(1)	22(1)	-2(1)	0(1)	-1(1)
C(17)	23(1)	27(1)	28(1)	2(1)	-3(1)	-1(1)
C(24)	31(1)	33(1)	29(1)	5(1)	-1(1)	3(1)
C(7)	27(1)	28(1)	40(1)	1(1)	5(1)	-3(1)
C(6)	37(1)	31(1)	29(1)	0(1)	1(1)	-3(1)
C(5)	32(1)	24(1)	29(1)	1(1)	-2(1)	-2(1)
C(21)	25(1)	37(1)	36(1)	6(1)	-2(1)	-1(1)
C(14)	24(1)	26(1)	25(1)	2(1)	-2(1)	1(1)
C(4)	40(1)	30(1)	48(1)	2(1)	-7(1)	-8(1)
C(12)	35(1)	35(1)	44(1)	2(1)	2(1)	1(1)
C(3)	37(1)	46(1)	47(1)	-1(1)	5(1)	-4(1)
C(22)	33(1)	37(1)	44(1)	8(1)	-3(1)	-9(1)
C(2)	32(1)	29(1)	36(1)	1(1)	-6(1)	-2(1)
C(25)	22(1)	31(1)	25(1)	2(1)	1(1)	-1(1)
C(8)	40(1)	32(1)	52(1)	-6(1)	9(1)	-2(1)
C(10)	42(1)	41(1)	87(2)	19(1)	10(1)	8(1)
C(11)	40(1)	50(1)	59(1)	15(1)	1(1)	8(1)
C(9)	45(1)	27(1)	88(2)	-2(1)	18(1)	3(1)

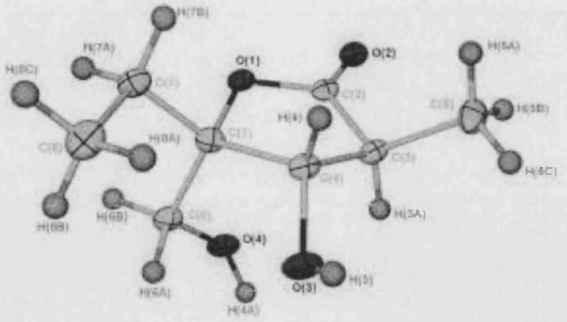


Table 1. Crystal data and structure refinement for **258**.

Identification code	c:\x-ray\kappa\k05rg1\maxus\k05rg1
Empirical formula	C8 H14 O4
Formula weight	174.19
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21
Unit cell dimensions	a = 5.4370(2)Å α = 90° b = 14.1610(6)Å β = 101.723(2)° c = 5.9280(2)Å γ = 90°
Volume	446.90(3) $Å^3$
Z	2
Density (calculated)	1.294 Mg/m^3
Absorption coefficient	0.103 mm^{-1}
F(000)	188
Crystal size	0.18 x 0.18 x 0.03 mm
Theta range for data collection	5.46 to 27.47°
Index ranges	-9<=h<=9, -19<=k<=19, -25<=l<=26
Reflections collected	8674
Independent reflections	2025 [R(int) = 0.0559]
Reflections observed (>2□)	1779
Data Completeness	0.989
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2025 / 1 / 116
Goodness-of-fit on F^2	1.149
Final R indices [I>2sigma(I)])]	R^1 = 0.0554 wR_2 = 0.0926
R indices (all data)	R^1 = 0.0679 wR_2 = 0.0959
Absolute structure parameter	0.3(13)
Largest diff. peak and hole	0.191 and -0.154 $eÅ^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for.U(eq) s defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
O(1)	8345(3)	8800(1)	9406(2)	31(1)

O(2)	9941(3)	7395(1)	8907(3)	37(1)
O(3)	3756(3)	8476(2)	12861(2)	41(1)
O(4)	3461(3)	8491(1)	7400(2)	39(1)
C(1)	6453(4)	9224(2)	10561(4)	32(1)
C(2)	8566(4)	7873(2)	9808(3)	31(1)
C(3)	6985(4)	7555(2)	11478(4)	33(1)
C(4)	6210(4)	8485(2)	12435(3)	31(1)
C(5)	8376(5)	6859(2)	13253(4)	45(1)
C(6)	4074(4)	9335(2)	8710(4)	35(1)
C(7)	7494(5)	10172(2)	11493(4)	40(1)
C(8)	5845(5)	10676(2)	12916(5)	47(1)

Table 3. Bond lengths [Å] and angles [°] for **258**.

O(1)-C(2)	1.335(3)	O(1)-C(1)	1.474(2)
O(2)-C(2)	1.210(3)	O(3)-C(4)	1.407(2)
O(4)-C(6)	1.427(3)	C(1)-C(7)	1.517(3)
C(1)-C(6)	1.525(3)	C(1)-C(4)	1.550(3)
C(2)-C(3)	1.506(3)	C(3)-C(5)	1.526(3)
C(3)-C(4)	1.527(3)	C(7)-C(8)	1.527(3)
C(2)-O(1)-C(1)	111.29(17)	O(1)-C(1)-C(7)	106.57(17)
O(1)-C(1)-C(6)	106.11(16)	C(7)-C(1)-C(6)	111.7(2)
O(1)-C(1)-C(4)	103.15(18)	C(7)-C(1)-C(4)	114.57(19)
C(6)-C(1)-C(4)	113.71(19)	O(2)-C(2)-O(1)	120.8(2)
O(2)-C(2)-C(3)	127.5(2)	O(1)-C(2)-C(3)	111.6(2)
C(2)-C(3)-C(5)	112.2(2)	C(2)-C(3)-C(4)	102.95(18)
C(5)-C(3)-C(4)	115.90(18)	O(3)-C(4)-C(3)	113.69(19)
O(3)-C(4)-C(1)	110.93(18)	C(3)-C(4)-C(1)	104.21(16)
O(4)-C(6)-C(1)	112.0(2)	C(1)-C(7)-C(8)	113.45(19)

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for **258**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}$

Atom	U11	U22	U33	U23	U13	U12
O(1)	28(1)	40(1)	28(1)	0(1)	12(1)	-5(1)
O(2)	38(1)	44(1)	31(1)	-7(1)	11(1)	-3(1)
O(3)	34(1)	71(1)	19(1)	-2(1)	9(1)	-13(1)
O(4)	33(1)	65(1)	20(1)	-2(1)	9(1)	-9(1)
C(1)	31(1)	43(1)	24(1)	0(1)	12(1)	-1(1)
C(2)	28(1)	41(2)	22(1)	-4(1)	3(1)	-8(1)
C(3)	33(1)	42(2)	22(1)	-2(1)	5(1)	-12(1)
C(4)	31(1)	44(1)	19(1)	-2(1)	5(1)	-7(1)
C(5)	59(2)	43(2)	31(1)	5(1)	5(1)	-5(1)
C(6)	34(1)	47(2)	26(1)	5(1)	13(1)	-3(1)
C(7)	38(1)	44(2)	42(1)	-3(1)	14(1)	-8(1)
C(8)	57(2)	49(2)	39(1)	-6(1)	17(1)	-6(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **258**.

Atom	x	y	z	U(eq)
H(3)	3822	8436	14286	60(8)
H(4A)	2238	8224	7801	41(7)
H(3A)	5445	7238	10591	39
H(4)	7423	8644	13891	38
H(5A)	9903	7157	14124	67
H(5B)	8828	6297	12464	67
H(5C)	7289	6676	14311	67
H(6A)	2658	9506	9449	41
H(6B)	4312	9856	7662	41
H(7A)	7681	10581	10186	48
H(7B)	9185	10075	12464	48
H(8A)	5700	10286	14248	71
H(8B)	4172	10782	11963	71
H(8C)	6606	11285	13450	71

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Publications

"Stereoselective synthesis of (*E*)-trisubstituted *alpha,beta*-unsaturated amides and acids." Feuillet, F. J. P.; Cheeseman, M.; Mahon, M. F.; Bull, S. D. *Organic & Biomolecular Chemistry* **2005**, *3*, 2976-2989.

"Stereoselective rearrangement of *beta*-hydroxy-*N*-acyloxazolidin-2-ones to afford *N*-2-hydroxyethyl-1,3-oxazinane-2,4-diones." Feuillet, F. J. P.; Niyadurupola, D. G.; Green, R.; Cheeseman, M.; Bull, S. D. *Synlett* **2005**, 1090-1094.

"A novel strategy for the asymmetric synthesis of chiral cyclopropane carboxaldehydes." Cheeseman, M.; Feuillet, F. J. P.; Johnson, A. L.; Bull, S. D. *Chemical Communications* **2005**, 2372-2374.

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"An efficient asymmetric synthesis of grenadamide." Green, R.; Cheeseman, M.; Duffill, S.; Merritt, A.; Bull, S. D. *Tetrahedron Letters* **2005**, *46*, 7931-7934.

ARTICLE

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Stereoselective synthesis of (*E*)-trisubstituted α,β-unsaturated amides and acids

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Potassium alkoxides of *N*-acyl-oxazolidin-2-one-*syn*-aldols undergo stereoselective elimination reactions to afford a range of trisubstituted (*E*)-α,β-unsaturated amides in >95% de, that may be subsequently converted into their corresponding (*E*)-α,β-unsaturated acids or (*E*)-α,β-unsaturated oxazolines in good yield. *syn*-Aldols derived from α,β-unsaturated aldehydes gave their corresponding trisubstituted (*E*)-α,β-unsaturated-amides with poorer levels of diastereocontrol, whilst there was a similar loss in (*E*)-selectivity during elimination of *syn*-aldols derived from chiral aldehydes. These elimination reactions proceed *via* rearrangement of the potassium alkoxide of the *syn*-aldol to a 1,3-oxazinane-2,4-dione enolate intermediate that subsequently eliminates carbon dioxide to afford a trisubstituted (*E*)-α,β-unsaturated amide. The (*E*)-selectivity observed during the E1cB-type elimination step has been rationalised using a simple conformational model that employs a chair-like transition state to explain the observed stereocontrol.

Introduction

(*E*)-2,3-Trisubstituted-α,β-unsaturated carboxylic acid derivatives are versatile synthetic fragments for natural product synthesis,[1] that also function as useful substrates for a wide range of asymmetric methodology.[2] They are most often prepared using highly stereoselective Wittig reactions, where reaction of an α-substituted-ester-ylid with an aldehyde affords the desired trisubstituted (*E*)-α,β-unsaturated ester in excellent yield.[3] Similar excellent levels of stereocontrol are also observed for Horner–Wadsworth–Emmons reactions, where anions of α-substituted-phosphonate esters also react with aldehydes in a highly (*E*)-selective manner.[4] Whilst less widely used in natural product synthesis, numerous other strategies have been developed for their stereoselective synthesis, including hydrocarboxylation of alkynes,[5] addition of carbanions to Baylis–Hillman adducts,[6] cross-metathesis approaches,[7] and the rearrangement of lithium ynolates.[8]

A wide range of aldol methodology is now available for the stereoselective synthesis of *syn*- or *anti*-α-alkyl-β-hydroxy-acid derivatives, and as a consequence, a number of elimination protocols has been developed for their stereoselective conversion into trisubstituted (*E*)-α,β-unsaturated acid derivatives. For example, Ohmizu *et al.* have shown that treatment of *anti*-α-alkyl-β-hydroxy-esters with EDCI and $CuCl_2$ in toluene at 80 °C results in *syn*-elimination to afford trisubstituted (*E*)-α,β-unsaturated esters, whilst treatment of the corresponding *syn*-α-alkyl-β-hydroxy-esters gave the alternative trisubstituted (*Z*)-α,β-unsaturated ester in high de.[9] Alternatively, treatment of α-alkyl-β-hydroxy-esters with excess triphenylphosphine and diethyl azodicarboxylate results in an *anti*-selective elimination reaction, with *syn*-α-alkyl-β-hydroxy-esters affording trisubstituted (*E*)-α,β-unsaturated esters, whilst *anti*-α-alkyl-β-hydroxy-esters gave their corresponding (*Z*)-isomers.[10] Bartoli *et al.* have reported that treatment of diastereoisomeric mixtures of *syn*-/*anti*-α-alkyl-β-hydroxy esters with $CeCl_3$ and NaI in refluxing acetonitrile gave trisubstituted (*E*)-esters in high de.[11] Similarly, Concellón *et al.* have described similar good levels of (*E*)-selectivity when samarium iodide is employed for the reductive elimination of mixtures of *syn*-/*anti*-α-halo-β-hydroxy-acid derivatives.[12] Mixtures of *syn*-/*anti*-α-alkyl-β-hydroxy-esters may also be dehydrated *via* step-wise protocols involving conversion to their corresponding tosylates/mesylates, followed by base-catalysed elimination to afford trisubstituted (*E*)-α,β-unsaturated esters in good de.[13] Only a few reports on the use of stereoselective versions of the Perkin reaction have been described, although Verkade *et al.* have described a potentially useful 'one-pot' protocol that employs a pro-azaphosphatrane base for the dehydrative aldol-condensation of an ester with an aldehyde to afford trisubstituted (*E*)-α,β-unsaturated esters in high de.[14]

Natural products that contain trisubstituted (*E*)-α,β-unsaturated-amide fragments also occur widely in nature,[15] whilst they have often been employed as structural motifs for the preparation of medicinally active compounds.[16] A number of different synthetic routes is available for their stereoselective synthesis, including direct amide formation from their corresponding (*E*)-acids[17] or (*E*)-esters,[18] Horner–Wadsworth–Emmons methodology,[19] aldol dehydration,[20] SmI_2 mediated elimination of α-chloro-β-hydroxy-amides or α,β-epoxy-amides,[21] or rearrangement of lithium ynolates.[22] The development of versatile protocols for their synthesis is therefore of great interest to the synthetic community. Consequently, we now report herein that potassium alkoxides of *N*-acyl-oxazolidin-2-one-*syn*-aldols undergo stereoselective elimination reactions to afford a highly practical route to trisubstituted (*E*)-α,β-unsaturated amides with good levels of stereocontrol. Part of this work has been communicated previously.[23]

Results and discussion

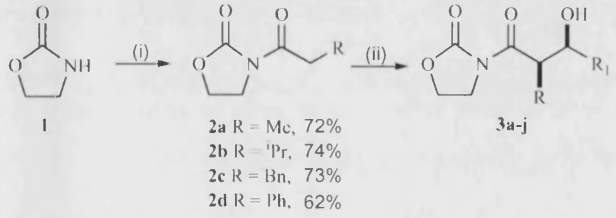
We have recently reported a novel aldol/cyclopropanation/*retro*-aldol strategy for the asymmetric synthesis of chiral cyclopropane carboxaldehydes in high de.[24] The success of this methodology required the development of conditions that would result in β-hydroxy-*N*-acyl-oxazolidin-2-ones undergoing a clean *retro*-aldol reaction to afford their respective *N*-acyl-oxazolidin-2-one and aldehyde fragments. In order to establish optimal conditions for this type of *retro*-aldol reaction, it was decided to employ a series of racemic β-hydroxy-*N*-acyl-oxazolidin-2-ones **3a–j** as simple model substrates to probe the steric and electronic requirements of this fragmentation pathway. Consequently, a series of four *N*-acyl-oxazolidin-2-ones **2a–d** were prepared in 62–74% yield *via* treatment of oxazolidin-2-one **1** in THF with 1.1 equivalents of *n*-BuLi at

Table 1 Yields of *syn*-aldols **3a–j**

Aldol	R	R_1	de (%)	Yield (%)[a]
3a	^{i}Pr	Cyclohexyl	>95	58
3b	Me	Ph	>95	69
3c	Me	Et	>95	31
3d	Bn	$Me(CH_2)_6$–	>95	74
3e	^{i}Pr	Et	>95	48
3f	^{i}Pr	Ph	>95	50
3g	^{i}Pr	*p*$MeOC_6H_4$–	>95	60
3h	Ph	Et	>95	37
3i	^{i}Pr	(*E*)–MeCH=CH–	>95	72
3j	Me	(*E*)–PhCH=CH–	>95	88

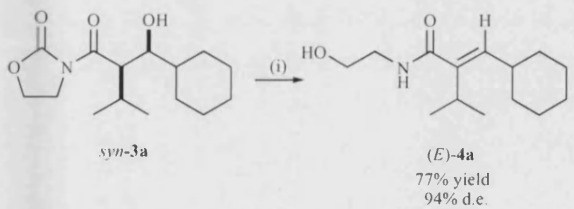
[a] Yields of *syn*-aldol products obtained in <70% were a result of unreacted *N*-acyl-oxazolidin-2-one **2a–d** being recovered at the end of the aldol reaction.

−78 °C, followed by addition of the appropriate acid chloride. After screening a range of boron sources and conditions, it was found that treatment of *N*-acyl-oxazolidin-2-ones **2a–d** with 9-BBN triflate (in hexanes) and $^i Pr_2NEt$ in CH_2Cl_2, followed by addition of the appropriate aldehyde at −78 °C, resulted in the formation of the desired *syn*-aldol products **3a–j**.[25] Examination of the ^{1}H NMR spectrum of each crude reaction product revealed the presence of desired *syn*-aldols **3a–j** in >95% de, which were purified to homogeneity by chromatography in poor to unoptimised 31–88% yields (Scheme 1, Table 1). The relative configuration of each of the racemic aldol products **3a–j** was assigned as *syn*- by analogy with literature precedent for the reaction of (*Z*)-boron-enolates of *N*-acyl-oxazolidin-2-ones in these types of aldol reactions.[26] This stereochemical assignment was subsequently confirmed for *syn*-aldol **3b** whose ^{1}H NMR spectrum was identical to the data previously reported for this diastereoisomer ($J_{(2,3)}$ = 3.0 Hz), whilst being clearly different from the ^{1}H NMR spectrum of its corresponding *anti*-aldol diastereoisomer ($J_{(2,3)}$ = 8.5 Hz).[27]



Scheme 1 *Reagents and conditions*: (i) *n*-BuLi, THF, −78 °C, KCH_2COCl; (ii) 9-BBN-OTf, $^i Pr_2NEt$, CH_2Cl_2, 0 to −78 °C, R_1CHO, CH_2Cl_2.

Attempts to establish anionic conditions that would result in *syn*-aldol **3a** undergoing a *retro*-aldol reaction under anionic conditions were unsuccessful, since treatment of *syn*-aldol **3a** with 1.5 equivalents of KHMDS in THF at −78 °C over a period of 2 hours resulted in an unexpected stereoselective elimination reaction to afford the trisubstituted α,β-unsaturated amide (*E*)-**4a** in 94% de, and in 77% isolated yield (Scheme 2). The geometry of the alkene functionality of (*E*)-**4a** was confirmed *via* X-ray crystallographic analysis that clearly revealed the *cis*-orientation of the α-iso-propyl group and the β-cyclohexane group (Fig. 1). Other aspects of the X-ray crystal structure of (*E*)-**4a** were



Scheme 2 *Reagents and conditions*: (i) KHMDS, THF, −78 °C.

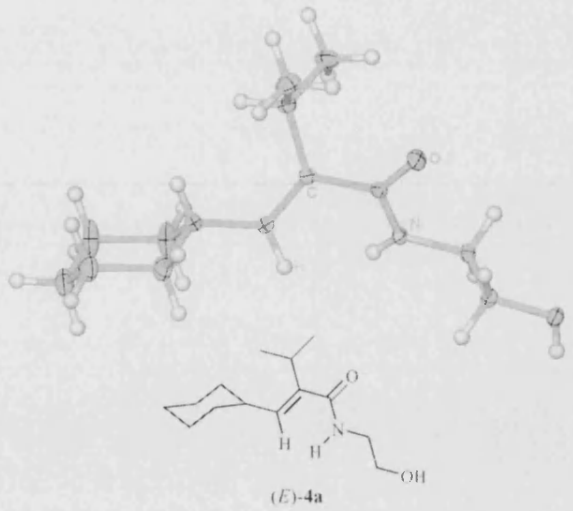
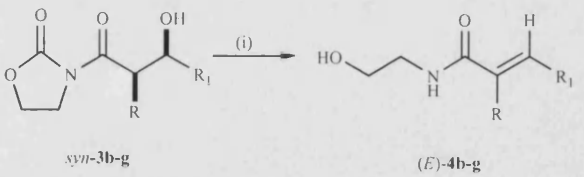


Fig. 1 One of the two molecules which comprise the asymmetric unit in the crystal structure of (*E*)-**4a**. Ellipsoids are depicted at the 30% probability level.

unremarkable, with crystal packing occurring *via* intermolecular hydrogen bonding between the primary hydroxyl groups of adjacent (*E*)-amide molecules.

In order to determine whether this elimination reaction was general in scope, the remaining series of *syn*-aldols **3b–g** was treated with 1.5 equivalents of KHMDS in THF at −78 °C for 2 hours, after which time the reaction was worked up with saturated $NH_4Cl_{(aq)}$. Examination of the crude ^{1}H NMR spectrum of each crude reaction product revealed that trisubstituted (*E*)-α,β-unsaturated amides **4b–g** had been formed in >90% de in each case, which were subsequently obtained in 67–99% yield after chromatographic purification (Scheme 3, Table 2). The structure of each (*E*)-α,β-unsaturated amide **4b–g** followed from comparison of their spectroscopic data with that of (*E*)-amide **4a**, whilst the alkene geometry of (*E*)-amides **4a–c** was confirmed *via* acidic hydrolysis to their known (*E*)-acids **26a–c** (*vide infra*). It is noteworthy that this simple elimination methodology appeared general in scope with linear and branched R substituents being tolerated at the α-position of *syn*-aldols **3a–g**, and with aliphatic and aromatic (neutral and electron rich) R_1-substituents being tolerated at their β-position (Scheme 1, Table 1). Attempts to carry out these elimination reactions at 0 °C resulted in the desired (*E*)-amides **4** being produced in inferior de; for example, treatment of *syn*-aldol **3b** with KHMDS in THF at 0 °C resulted in (*E*)-amide **4b** being produced in only 80% de.



Scheme 3 *Reagents and conditions*: (i) KHMDS, THF, −78 °C.

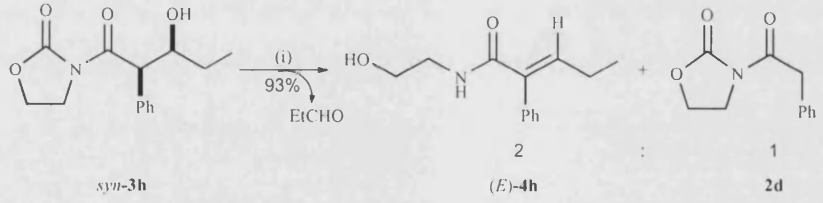
Table 2 Yields for synthesis of (*E*)-amides **4b–g**

Amide	R	R_1	de (%)	Yield (%)
4b	Me	Ph	>95	91
4c	Me	Et	>95	67
4d	Bn	$Me(CH_2)_6$–	92	91
4e	^{i}Pr	Et	>95	99
4f	^{i}Pr	Ph	92	90
4g	^{i}Pr	*p*$MeOC_6H_4$–	90	88

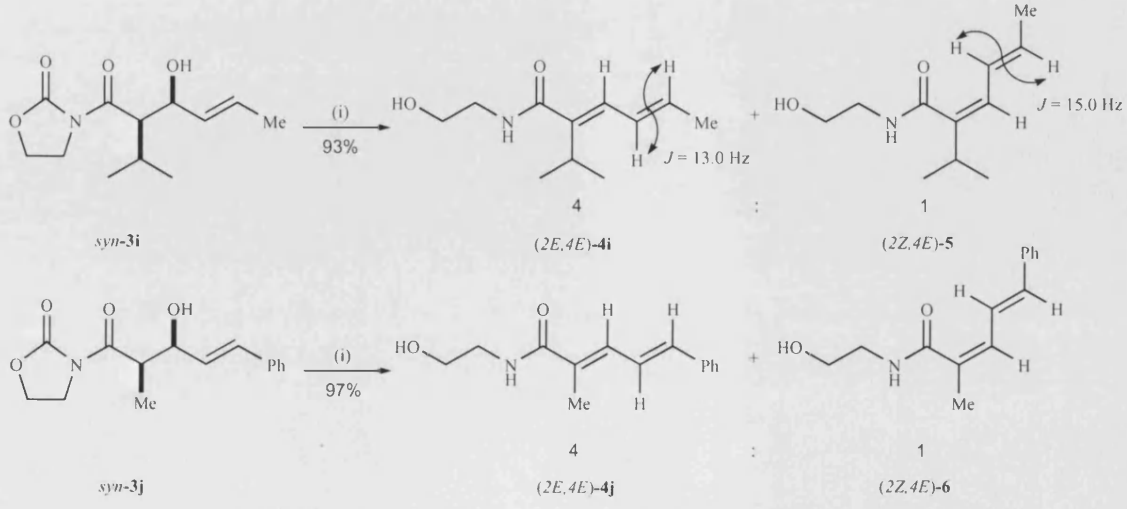
Further investigations revealed that elimination of *syn*-aldol **3h** containing an α-phenyl group under these conditions, gave a mixture of the desired (*E*)-amide **4h** (>95% de) and *N*-phenylacetyl-oxazolidin-2-one **2d** in a 2 : 1 ratio, which was purified by chromatography to afford (*E*)-**4h** in 47% yield. Presumably, *N*-phenylacetyl-oxazolidin-2-one **2d** arises from a competing *retro*-aldol reaction as originally conceived, where the potassium alkoxide of *syn*-aldol **3h** had fragmented to afford (*E*)-**4h** and propionaldehyde (not isolated). It is likely that the *retro*-aldol reaction of the alkoxide of *syn*-aldol **4h** is more favoured than for the other *syn*-aldols **4a–g** investigated in this study, because the enolate of *N*-phenylacetyloxazolidin-2-one **2d** is stabilised by the presence of its α-phenyl substituent (Scheme 4).

Treatment of *syn*-aldols **3i** and **3j** with KHMDS in CH_2Cl_2 at −78 °C afforded (2*E*,4*E*)-α,β,γ,δ-unsaturated amides **4i** and **4j** in a stereoselective manner, however they were both formed with poorer levels of stereocontrol. Thus, treatment of *syn*-aldol **3i** with KHMDS at −78 °C resulted in (2*E*,4*E*)-α,β,γ,δ-unsaturated amide **4i**, and its geometric isomer (2*Z*,4*E*)-α,β,γ,δ-unsaturated amide **5**, in a 4 : 1 ratio, and in a combined 93% yield (Scheme 5). Attempted chromatographic purification of these geometric isomers over silica gel was unsuccessful, however (2*E*,4*E*)-**4i** and (2*Z*,4*E*)-**5** could be partially separated *via* chromatography over silica gel doped with silver nitrate.[28] The presence of the (2*Z*)-alkene geometry of (2*Z*,4*E*)-**5** was confirmed from examination of its ^{1}H NMR spectrum which revealed a coupling constant of $J_{(4,5)}$ = 15.0 Hz, that was similar in value to that observed for (2*E*,4*E*)-**4i** of $J_{(4,5)}$ = 13.0 Hz. Similarly, treatment of *syn*-aldol **3j** with KHMDS in THF at −78 °C also gave a 4 : 1 mixture of (2*E*,4*E*)-**4j** and (2*Z*,4*E*)-**6** in a combined 97% yield (Scheme 5).[29] Fractional recrystallisation of this mixture of geometric isomers from ethyl acetate afforded the major amide (2*E*,4*E*)-**4j** in 64% isolated yield, whose alkene geometry was confirmed *via* hydrolysis to its known parent (2*E*,4*E*)-acid **27** (*vide infra*). Therefore, it appears that elimination of *syn*-aldols derived from α,β-unsaturated aldehydes under these conditions occurs with intrinsically poorer levels of stereocontrol than for the other *syn*-aldols **3a–g** investigated in this study.

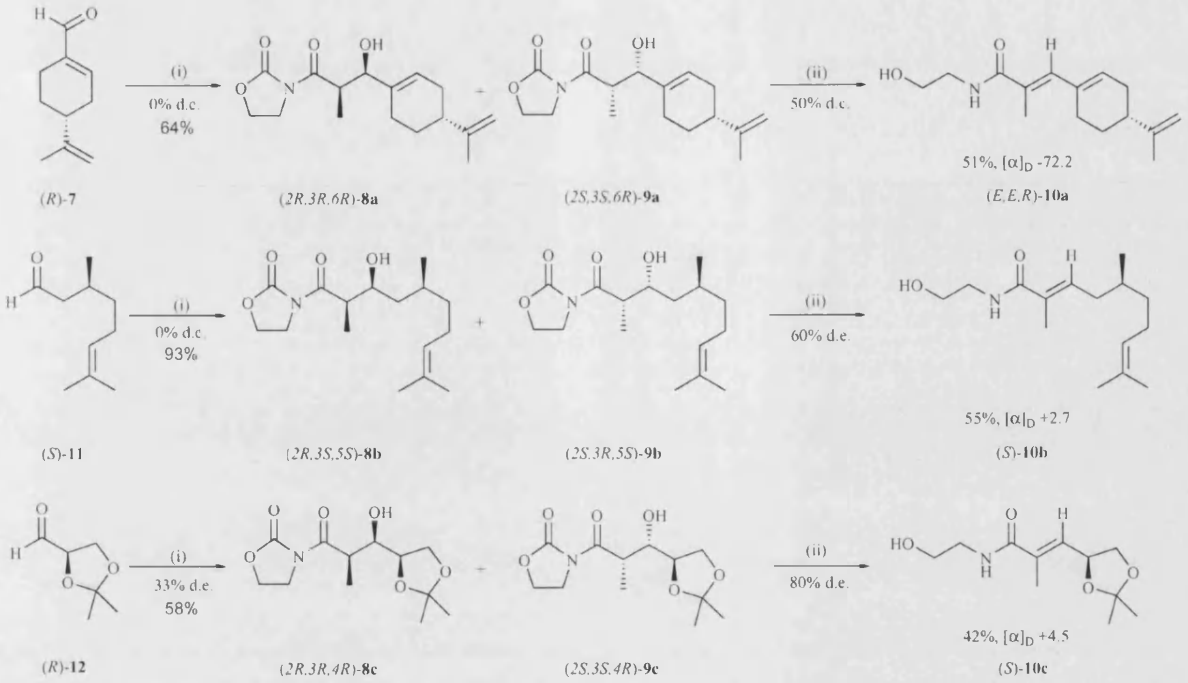
In order to demonstrate that this elimination methodology was applicable to the stereoselective synthesis of trisubstituted-(*E*)-amides of potential use as building blocks for natural product synthesis, we next explored its use for the preparation of three trisubstituted (*E*)-α,β-unsaturated amides **10a–c** derived from chiral aldehydes (Scheme 6). Reaction of the (*Z*)-boron enolate of *N*-propionyl-oxazolidin-2-one **2a** with perillaldehyde (*R*)-**7** (90% pure) resulted in a 1 : 1 mixture of *syn*-aldol diastereoisomers **8a/9a** in 64% yield.[30] Treatment of this mixture of *syn*-aldols **8a/9a** with KHMDS in THF at −78 °C resulted in a clean elimination reaction to afford α,β,γ,δ-unsaturated amide (*E*,*E*,*R*)-**10a** in 50% de, which was purified to homogeneity *via* chromatography in 51% yield. Since elimination of *syn*-aldols derived from α,β-unsaturated aldehydes had been shown to afford (*E*,*E*)-unsaturated-amides in inferior de, we next reacted the (*Z*)-boron enolate of **2a** with citronellal (*S*)-**11** (96% pure) to afford an inseparable 1 : 1 mixture of diastereoisomeric *syn*-aldols **8b/9b** in 93% yield. This mixture was subsequently treated with KHMDS in THF at −78 °C to afford (*E*,*S*)-amide **10b** in 60% de, that was purified to homogeneity *via* chromatography in 55% yield. The moderate diastereocontrol observed in this elimination reaction was somewhat surprising, since elimination of the related *syn*-aldol **3d**, which also contained a long alkyl chain at its β-position, gave its corresponding (*E*)-amide **4d** in 92% de. Finally, reaction of the (*Z*)-boron enolate of **2a** with 1.1 equivalents of D-glyceraldehyde acetonide (*R*)-**12** afforded a 2 : 1 mixture of *syn*-aldol diastereoisomers **8c/9c** that were co-isolated in 58% yield after chromatography over silica.[31] The 2 : 1 mixture of *syn*-aldols **8c/9c** produced in this reaction is likely to result from attack of the boron-enolate of **2a** at the carbonyl of (*R*)-**12** occurring under substrate control, where formation of the major aldol diastereoisomer (stereochemistry not determined) is favoured by the stereodirecting effect of the α-stereogenic centre of aldehyde (*R*)-**12**. Generation of the potassium alkoxides of *syn*-aldols **8c/9c** *via* treatment of this mixture with KHMDS in THF at −78 °C, resulted in the formation of (*E*,*S*)-amide **10c** in 80% de, which was purified to homogeneity *via* chromatography in 42% isolated yield.[32]



Scheme 4 *Reagents and conditions*: (i) KHMDS, THF, −78 °C.



Scheme 5 *Reagents and conditions*: (i) KHMDS, THF, −78 °C.



Scheme 6 *Reagents and conditions*: (i) **2a**, 9-BBN-OTf, $^{i}Pr_2NEt$, CH_2Cl_2, 0 to −78 °C; (ii) KHMDS, THF, −78 °C.

Therefore, whilst the potassium alkoxides of *syn*-aldols **8a–c**/**9a–c** derived from chiral aldehydes eliminated to afford their desired trisubstituted α,β-unsaturated amides (*E*)-**10a–c**, it is clear that these reactions had proceeded with inferior levels of (*E*)-stereocontrol to those previously observed for the simpler *syn*-aldols **4a–g**.

Mechanism of the stereoselective elimination reaction of *syn*-aldols

It is well known that sterically unhindered *N*-acyloxazolidin-2-ones can undergo endocyclic ring cleavage *via* either inter- or intramolecular attack of alkoxide nucleophiles at their oxazolidin-2-one carbonyl groups.[33] Consequently, it was proposed that the high diastereoselectivities observed for the elimination of *syn*-aldols **3** could be explained by a novel intramolecular cyclisation/E1cB-type elimination mechanism as shown in Fig. 2. In this mechanism, deprotonation of *syn*-aldol **11** would result in potassium alkoxide **12**, that would then undergo intramolecular attack at the oxazolidin-2-one carbonyl resulting in *O*–*O* carbonyl migration to afford 1,3-oxazinane-2,4-dione alkoxide intermediate **13**. Subsequent anion equilibration of alkoxide **13** would then give 1,3-oxazinane-2,4-dione enolate **14** that would then undergo stereoselective elimination of carbon dioxide to afford the trisubstituted secondary amide (*E*)-**15** in high de (Fig. 2).

In order to provide evidence for this mechanism, it was proposed that treatment of 1,3-oxazinane-2,4-dione **16** with KHMDS in THF at −78 °C should result in stereoselective elimination to afford trisubstituted amide (*E*)-**4b** in an identical de to that observed for elimination of its parent *syn*-aldol **3b**. We have reported previously that zinc alkoxides of α-alkyl-β-hydroxy-*N*-acyl-oxazolidin-2-ones undergo clean rearrangement to afford 1,3-oxazinane-2,4-diones,[34] and as a consequence *syn*-1,3-oxazinane-2,4-dione **16** was prepared in 97% yield *via* treatment of *syn*-aldol **3b** with 10 mol% of Et_2Zn in CH_2Cl_2 at room temperature. Subsequent treatment of *syn*-1,3-oxazinane-2,4-dione **16** with KHMDS in THF at −78 °C gave amide (*E*)-**4b** in an identical >95% de to that previously observed for elimination of the potassium alkoxide of *syn*-aldol **3b** (Scheme 7).[35] This observation therefore provides good evidence that the potassium alkoxide of 1,3-oxazinane-2,4-diones **13**, and their corresponding enolates **14**, are key intermediates in these stereoselective elimination reactions (Fig. 2).

We next confirmed that the loss in stereoselectivity observed during elimination of the potassium alkoxides of *syn*-aldol **3i** was occurring during elimination of carbon dioxide from the enolate of *syn*-1,3-oxazinane-2,4-dione intermediate **17**. Thus, treatment of *syn*-aldol **3i** with 10 mol% Et_2Zn in CH_2Cl_2 resulted in a zinc alkoxide that cleanly rearranged to afford its *syn*-1,3-oxazinane-2,4-dione **17** in >95% de with no loss of stereochemical integrity at either its α- or β-stereocentres. *syn*-1,3-Oxazinane-2,4-dione **17** was treated with KHMDS in THF at −78 °C under conditions used previously for the direct elimination of *syn*-aldol **3i**, to afford an identical 4 : 1 ratio of (2*E*,4*E*)-α,β-unsaturated amide **4i** and (2*Z*,4*E*)-α,β-unsaturated amide **5** in an excellent 88% yield (Scheme 8). Therefore, it appears that the loss of stereocontrol observed for *syn*-aldol **3i** occurs exclusively during elimination of carbon dioxide from the enolate derived from *syn*-1,3-oxazinane-2,4-dione intermediate **17**.

Finally, we explored the elimination of the corresponding *anti*-aldol **18** which was prepared *via* treatment of **2a** with $MgCl_2$, TMSCl, Et_3N and benzaldehyde in EtOAc in an unoptimised 33% yield, according to Evans' recently published procedure.[36] Treatment of *anti*-aldol **18** with KHMDS in THF at −78 °C afforded amide (*E*)-**4b** in >95% de, a value identical to that

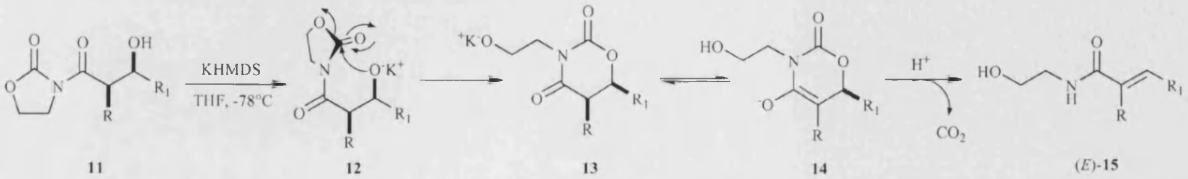
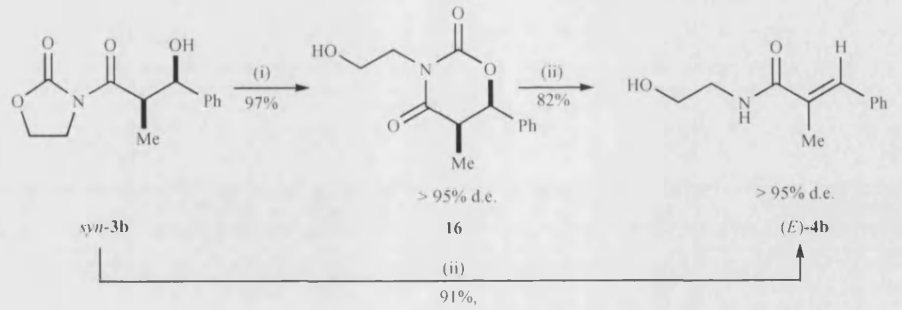
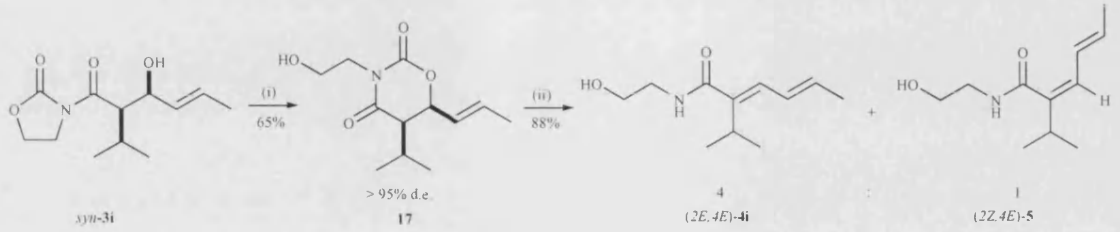


Fig. 2 Intramolecular cyclisation/E1cB-elimination mechanism for the stereoselective elimination of *syn*-aldol **11**.



Scheme 7 *Reagents and conditions*: (i) Et_2Zn, THF, rt; (ii) KHMDS, THF, −78 °C.



Scheme 8 *Reagents and conditions*: (i) 10 mol% Et_2Zn, THF, rt; (ii) KHMDS, THF, −78 °C.

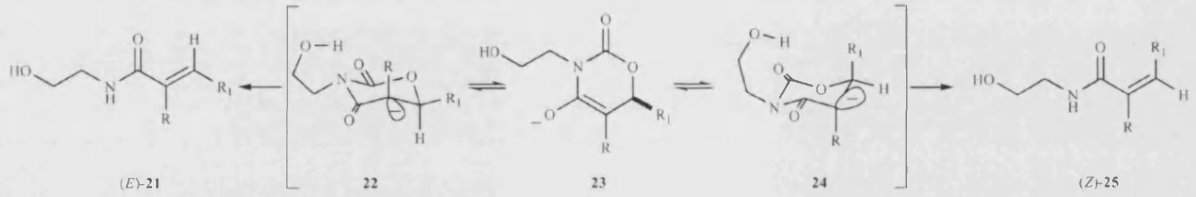
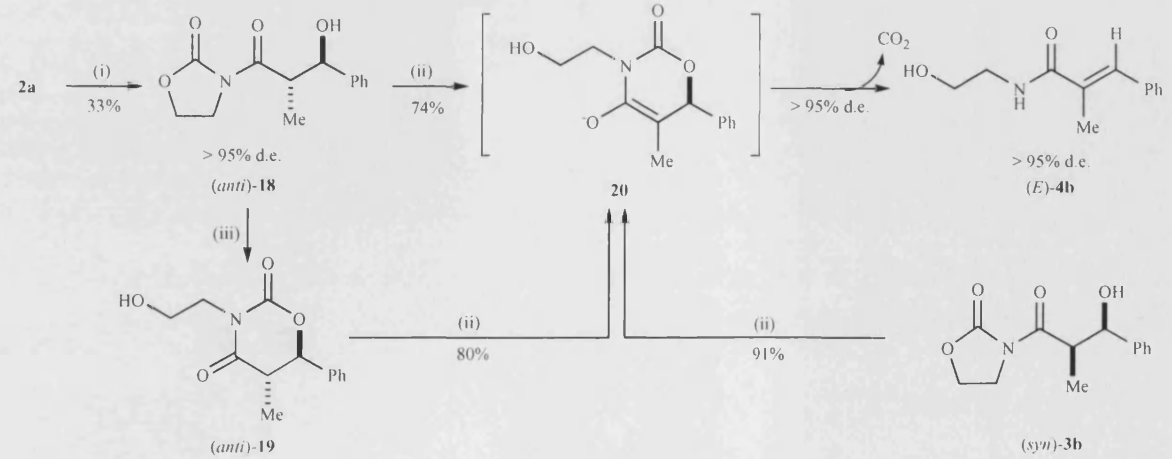


Fig. 3 Simple conformational model to explain (*E*)-selectivity in elimination reaction.

observed previously for elimination of the corresponding *syn*-aldol **3b** under the same conditions (Scheme 9). Furthermore, treatment of *anti*-aldol **18** with Et_2Zn in CH_2Cl_2 resulted in rearrangement to afford the corresponding *anti*-1,3-oxazinane-2,4-dione **19** in >95% de, which on treatment with KHMDS in THF at −78 °C also afforded amide (*E*)-**4b** in >95% de (Scheme 9). These observations are therefore clearly consistent with the key elimination step of both *anti*-aldol **18** and *syn*-aldol **3b** occurring *via* an E1cB-type mechanism, in which a common enolate intermediate **20** eliminates CO_2 to afford the α,β-unsaturated amide (*E*)-**4b** in high de (Scheme 9).

Whilst it is likely that the key E1cB-type elimination reactions of the 1,3-oxazinane-2,4-dione enolate **23** occur *via* a concerted reaction mechanism, the observed (*E*)-selectivity in these elimination reactions may be rationalised using a simple conformational model that compares the relative energies of transition state intermediates **22** and **24** (Fig. 3). In the case of transition state **22** that leads to (*E*)-amide **21**, concerted elimination of carbon dioxide from a cyclic ring system requires overlap of an equatorial C_5-carbanion with the σ^*-orbital of the C_6–O bond, which can only occur from a chair conformer in which the C_5–R group occupies an axial position, and the C_6–R_1 group occupies an equatorial position. This compares with transition state **24** that leads to (*Z*)-amide **25**, where a similar orbital alignment results in a chair conformer in which both the C_5–R group and C_6–R_1 substituents both occupy axial positions. Since transition state **22** contains only one axial substituent, it is likely to be lower in energy than transition state **24** which contains two axial substituents, and as a consequence formation of (*E*)-amide **21** is favoured. Whilst this 'carbanion' model

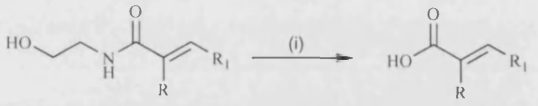


Scheme 9 *Reagents and conditions*: (i) $MgCl_2$, TMSCl, Et_3N, PhCHO, EtOAc; (ii) KHMDS, THF, −78 °C; (iii) 10 mol% Et_2Zn, THF, rt.

is clearly an over-simplification of the concerted elimination processes that are likely to be occurring in these elimination reactions, similar electronic and steric considerations are likely to be operating to maximise orbital overlap in the transition state that preferentially leads to the formation of (*E*)-amides in these reactions. However, it is also clear from the poorer levels of stereocontrol (50–80% de) observed for the elimination of *syn*-aldols derived from α,β-unsaturated aldehydes and chiral aldehydes, that subtle changes in the conformation and/or electron density of the transition states of these E1$_c$B-type reactions can result in significant losses in (*E*)-selectivity.

Synthesis of (*E*)-α,β-unsaturated carboxylic acids and (*E*)-α,β-unsaturated oxazolines

Having shown that this elimination methodology afforded an excellent general route to (*E*)-trisubstituted α,β-unsaturated amides, their conversion to other carboxylic acid derivatives was explored in order to demonstrate the synthetic versatility of this methodology. Five representative (*E*)-α,β-unsaturated amides **4a–d** and **4j** were refluxed in 6 M $HCl_{(aq)}$ for 5 hours to afford their corresponding (*E*)-α,β-unsaturated acids **26a–d** and **27** respectively in 77–99% isolated yield (Scheme 10, Table 3).[37] Importantly, examination of the ^{1}H NMR spectra of the crude reaction products of these hydrolysis reactions revealed that all of the α,β-unsaturated acids had been produced as single isomers with no evidence of any alkene migration having occurred under the strong acid conditions used for hydrolysis. The structures of α,β-unsaturated acids (*E*)-**26b** and (*E*)-**26c** were confirmed *via* comparison with commercially available samples of (*E*)-2-methylpentenoic acid and (*E*)-2-methyl-3-phenylpropenoic acid respectively, whilst spectroscopic data for (*E*)-**26a** and (*E*)-**27** were identical to previous literature reports.[38,39]



4a-d, 4j **26a-d, 27**

Scheme 10 *Reagents and conditions*: (i) 6 M $HCl_{(aq)}$.

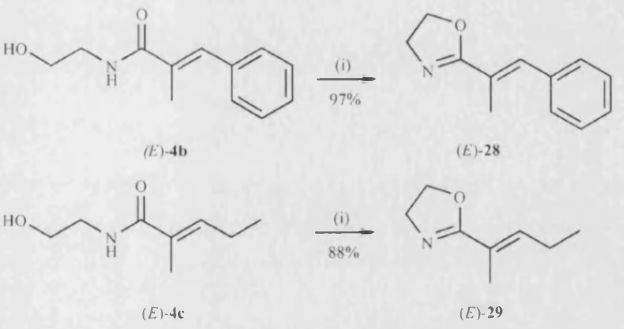
Table 3 Yields for synthesis of (*E*)-acids **26a–d** and **27**

Acid	R	R_1	de (%)	Yield (%)
26a	^{i}Pr	Cyclohexyl	>95	99
26b	Me	Ph	>95	95
26c	Me	Et	>95	91
26d	Bn	$Me(CH_2)_6$–	>95	95
27	Me	(*E*)–PhCH=CH–	>95	77

The synthetic potential of this methodology was further demonstrated *via* cyclisation of the *N*-hydroxyamide fragment of (*E*)-amides **4b** or **4c** to afford their corresponding trisubstituted (*E*)-α,β-unsaturated oxazolines (*E*)-**28** and (*E*)-**29**. Thus, addition of thionyl chloride (5 eq.) in a dropwise fashion to an ice-cold solution of α,β-unsaturated amides **4b** and **4c** in CH_2Cl_2, resulted in the desired oxazolines (*E*)-**28** and (*E*)-**29** in 97% and 88% yield respectively (Scheme 11). It should be noted that these types of (*E*)-α,β-unsaturated oxazolines are useful synthetic intermediates that are easily converted into their corresponding (*E*)-α,β-unsaturated acids, alcohols and aldehydes using known literature procedures.[40]

Conclusion

In conclusion, we have demonstrated that potassium alkoxides of *N*-acyl-oxazolidin-2-one derived-*syn*-aldols undergo stereoselective elimination reactions to afford a range of trisubstituted (*E*)-α,β-unsaturated amides in excellent de, that could be easily converted into their corresponding (*E*)-α,β-unsaturated acids or



Scheme 11 *Reagents and conditions*: (i) $SOCl_2$, CH_2Cl_2, 0 °C.

(*E*)-α,β-unsaturated oxazolines in good yield. Alkoxides of *syn*-aldols derived from α,β-unsaturated aldehydes were eliminated to afford their corresponding trisubstituted (*E*)-α,β-unsaturated-amides in an inferior 80% de, whilst there was also a similar loss in (*E*)-selectivity during elimination of more complex *syn*-aldols derived from chiral aldehydes. These elimination reactions proceed *via* rearrangement of their *syn*-aldol alkoxide to a 1,3-oxazinane-2,4-dione enolate intermediate that subsequently eliminates carbon dioxide to afford a trisubstituted (*E*)-α,β-unsaturated amide. The (*E*)-selectivity observed during the critical E1cB-type elimination step of this reaction has been rationalised using a simple conformational model that employs chair-like transition states to explain the observed stereocontrol.

Experimental

General experimental

All reactions were carried out under nitrogen or argon using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen. THF was distilled from sodium/benzophenone ketyl, whilst CH_2Cl_2 was distilled from CaH_2 under nitrogen. All other reagents were used as supplied without further purification. Flash column chromatography was performed on silica gel (Kieselgel 60). TLC was performed on Merck aluminium sheets coated with 0.2 mm silica gel 60 F254. Plates were visualised either by UV light (254 nm), iodine, ammonium molybdate (7% solution in ethanol) or potassium permanganate (1% in 2% aqueous acetic acid, containing 7% potassium carbonate). Infra red spectra were recorded as thin films or KBr discs using a Perkin-Elmer PARAGON 1000 FT-IR spectrometer, with selected peaks reported in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer. Chemical shifts are reported in parts per million (ppm) and are referenced to the residual solvent peak, with coupling constants (*J*) measured in Hertz. Low resolution mass spectra (*m/z*) were recorded on either a Finnigan MAT 8340 instrument or a Finnigan MAT 900 XLT instrument. Major peaks are listed with intensities quoted as percentages of the base peak. Accurate mass measurements were recorded on a Finnigan MAT 900 XLT instrument. Optical rotations were recorded on an Optical Activity Ltd AA-10 automatic polarimeter, using a path length of 10 cm, in spectroscopic grade solvents (Aldrich), with concentrations (*c*) given in g per 100 cm^3, solvent and temperature as recorded. Melting points were recorded on a Büchi 535 melting point apparatus and are uncorrected. Elemental analyses were performed using an Exeter Analytical Inc CE-440 Elemental analyser. Single crystal X-ray diffraction data were collected on a Nonius Kappa CCD machine. Structural determination and refinement were achieved using the SHELZ suite of programmes; drawings were produced using ORTEX.

General procedure A: preparation of *N*-acyl-oxazolidin-2-ones

A solution of *n*-butyllithium in hexanes (1.1 eq.) was added dropwise *via* syringe to a stirred solution of oxazolidin-2-one

1 (1 eq.) in THF at −78 °C under a nitrogen atmosphere and the mixture was allowed to stir for 15 minutes. The appropriate acid chloride (1.1 eq.) was then added at −78 °C. The reaction was stirred at this temperature for 2 hours and allowed to warm to room temperature over a 1 hour period. Saturated $NH_4Cl_{(aq)}$ was added and the reaction extracted with CH_2Cl_2 (× 3). The combined organic extracts were washed with $NaHCO_{3(aq)}$, dried ($MgSO_4$), and concentrated *in vacuo* to afford the desired *N*-acyl oxazolidin-2-one.

***General procedure B*: preparation of *N*-acyl-oxazolidin-2-one-*syn*-aldols**

A 0.5 M solution of 9-BBN-OTf in hexanes (1.2 eq.) was added *via* syringe to a stirred solution of *N*-acyloxazolidin-2-one (1 eq.) in CH_2Cl_2 at 0 °C and allowed to stir at this temperature for 5 minutes. *N*,*N*-diisopropylethylamine (1.4 eq.) was added, the reaction was stirred for 25 minutes at 0 °C before cooling to −78 °C. An aldehyde (1.1 eq.) was then added, the reaction was stirred for 2 hours and allowed to warm to 0 °C for 30 minutes. pH 7.0 phosphate buffer was added, allowed to stir for 5 min and a 2 : 1 solution of methanol–hydrogen peroxide added dropwise. The reaction was extracted with CH_2Cl_2 (× 3) and the combined organic extracts were washed with $NaHCO_{3(aq)}$, brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired *syn*-aldol.

***General procedure C*: preparation of trisubstituted (*E*)-α,β-unsaturated amides**

A 0.5 M solution of KHMDS in toluene (1.5 eq.) was added dropwise to a stirred solution of *syn*-aldol (1 eq.) in THF at −78 °C under nitrogen, and the reaction was stirred at −78 °C for two hours. Saturated $NH_4Cl_{(aq)}$ was added and the reaction was extracted with CH_2Cl_2 (× 3). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford the desired (*E*)-α,β-unsaturated amide.

***General procedure D*: preparation of 1,3-oxazinane-2,4-diones**

A 1.0 M solution of Et_2Zn in toluene (0.1 eq.) was added dropwise to a stirred solution of *syn*-aldol (1 eq.) in CH_2Cl_2 at room temperature, and the reaction was stirred for 2 hours. Saturated $NH_4Cl_{(aq)}$ was added and the reaction was extracted with CH_2Cl_2 (× 3). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford the desired *syn*-1,3-oxazinane-2,4-dione.

***General procedure E*: preparation of trisubstituted (*E*)-α,β-unsaturated acids**

An (*E*)-α,β-unsaturated amide was refluxed in 6.0 M HCl for five hours. The reaction mixture was allowed to cool to room temperature, saturated with sodium chloride, and extracted with ethyl acetate (5 × 10 ml). The combined organic layers were dried over magnesium sulfate and the solvent was removed *in vacuo* to afford the desired (*E*)-α,β-unsaturated carboxylic acid.

***General procedure F*: preparation of trisubstituted (*E*)-α,β-oxazolines**

Thionyl chloride (5 eq.) was added dropwise to a stirred solution of α,β-unsaturated amide (1 eq.) in CH_2Cl_2 in an ice bath, and the reaction mixture was stirred for 2 hours at this temperature. A 5.0 M solution of NaOH (3 mL) was added dropwise and the reaction was extracted with CH_2Cl_2 (× 3). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford the desired (*E*)-α,β-unsaturated oxazoline.

3-Propionyl-1,3-oxazolidin-2-one 2a[33]. Reaction of oxazolidin-2-one **1** (5.0 g, 57.47 mmol) with a 2.5 M solution of *n*-butyllithium in hexanes (25.30 mL, 63.2 mmol) and propionyl chloride (5.16 g, 63.2 mmol) in THF (250 mL), according to general procedure A, afforded after recrystallisation from hot ethyl acetate the title compound **2a** (5.940 g, 41.54 mmol) in 72% yield as a white crystalline solid, mp 77–79 °C (lit,[33] 80–81 °C); ν_{max} (KBr disc)/cm^{-1} 1773 (C=O)$_{ox}$, 1700 (C=O); δ_H(300 MHz, $CDCl_3$) 1.17 (3H, t, *J* 7.5, CH_2CH_3), 2.94 (2H, q, *J* 7.5, CH_2CH_3), 4.02 (2H, app t, *J* 8.0, CH_2N), 4.42 (2H, app t, *J* 8.0, CH_2O); δ_C($CDCl_3$) 8.7, 29.1, 42.9, 62.4, 154.0, 174.6; *m*/*z* (EI$^{+\bullet}$) 143 (49, M$^{+\bullet}$), 57 (100%, $CH_3CH_2CO^+$); HRMS (FAB$^+$) $C_6H_9NO_3$ [MH$^+$] requires 143.0577; found 143.0574.

3-(3-Methylbutanoyl)-1,3-oxazolidin-2-one 2b[41]. Reaction of oxazolidin-2-one **1** (9.905 g, 113.85 mmol) with a 2.5 M solution of *n*-butyllithium in hexanes (50.10 mL, 125.23 mmol) and isovaleryl chloride (21.50 mL, 125.23 mmol) in THF (500 mL), according to general procedure A, afforded after purification through silica gel chromatography (40% ethyl acetate–petrol) the title compound **2b** (14.408 g, 84.26 mmol) in 74% yield as a colourless oil, ν_{max} (neat)/cm^{-1} 1779 (C=O)$_{ox}$, 1699 (C=O); δ_H(300 MHz, $CDCl_3$) 0.99 (6H, d, *J* 7.0, $CH(CH_3)_2$), 2.18 (1H, m, *J* 7.0, $CH(CH_3)_2$), 2.81 (2H, d, *J* 7.0, $CH_2{}^iPr$), 4.03 (2H, app t, *J* 8.0, CH_2N), 4.42 (2H, app t, *J* 8.0, CH_2O); δ_C($CDCl_3$) 22.8, 25.3, 42.9, 43.9, 62.3, 153.9, 173.2; *m*/*z* (CI$^+$, iso-butane) 172 (85, MH$^+$), 129 (82, MH$^+$–$CH(CH_3)_2$), 85 (100%); HRMS (FAB$^+$) $C_8H_{14}NO_3$ [MH$^+$] requires 172.0974; found 172.0974.

3-(3-Phenylpropanoyl)-1,3-oxazolidin-2-one 2c[42]. Reaction of oxazolidin-2-one **1** (1.496 g, 17.20 mmol) with a 2.5 M solution of *n*-butyllithium in hexanes (7.60 mL, 18.91 mmol) and phenylpropionyl chloride (2.80 mL, 18.91 mmol) in THF (90 mL), according to general procedure A, afforded after purification through silica gel chromatography (20% ethyl acetate–petrol) the title compound **2c** (2.765 g, 12.63 mmol) in 73% yield as a white solid, mp 100–101 °C; ν_{max} (KBr disc)/cm^{-1} 3008 (C–H)$_{ar}$, 1765 (C=O)$_{ox}$, 1692 (C=O); δ_H(300 MHz, $CDCl_3$) 2.91 (2H, t, *J* 7.5, CH_2CH_2Ph), 3.17 (2H, t, *J* 7.5, CH_2CH_2Ph), 3.90 (2H, app t, *J* 8.0, CH_2N), 4.29 (2H, app t, *J* 8.0, CH_2O), 7.09–7.24 (5H, m, Ar–*H*); δ_C($CDCl_3$) 30.6, 37.2, 42.9, 62.5, 126.6, 128.8, 128.9, 140.9, 153.9, 172.9; *m*/*z* (EI$^{+\bullet}$) 219 (55, M$^{+\bullet}$), 132 (27, $PhCH_2CH_2CO^+$), 104 (100), 88 (87, M$^{+\bullet}$–$PhCH_2CH_2CO^\bullet$); HRMS (ES$^+$) $C_{12}H_{17}N_2O_3$ [MNH$_4^+$] requires 237.1234; found 237.1237.

3-(2-Phenylacetyl)-1,3-oxazolidin-2-one 2d[43]. Reaction of oxazolidin-2-one **1** (9.90 g, 113.79 mmol) with a 1.6 M solution of *n*-butyllithium in hexanes (78.20 mL, 125.17 mmol) and phenyl acetyl chloride (21.50 mL, 125.17 mmol) in THF (500 mL), according to general procedure A, afforded after purification through silica gel chromatography (20% ethyl acetate–petrol) the title compound **2d** (14.404 g, 70.26 mmol) in 62% yield as a white solid, mp 61–63 °C (lit,[43] 64–65 °C); ν_{max} (KBr disc)/cm^{-1} 3010 (C–H)$_{ar}$, 1773 (C=O)$_{ox}$, 1696 (C=O); δ_H(300 MHz, $CDCl_3$) 3.92 (2H, app t, *J* 8.0, CH_2N), 4.25 (2H, s, CH_2Ph), 4.29 (2H, app t, *J* 8.0, CH_2O), 7.26–7.31 (5H, m, Ar–*H*); δ_C($CDCl_3$) 43.2, 47.8, 63.2, 128.1, 129.4, 130.0, 131.6, 154.7, 172.3; *m*/*z* (EI$^{+\bullet}$) 205 (30, M$^{+\bullet}$), 118 (100), 91 (60%, $PhCH_2^+$); HRMS (ES$^+$) $C_{11}H_{11}NO_3$ [MH$^+$] requires 205.0739; found 205.0742.

***syn*-3-{2-[Cyclohexyl(hydroxy)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one 3a.** Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one **2b** (1.500 g, 8.77 mmol) with a 0.5 M solution of 9-BBN-OTf in hexanes (21.11 mL, 10.53 mmol), *N*,*N*-diisopropylethylamine (1.99 mL, 11.40 mmol) and cyclocarboxaldehyde (1.17 mL, 9.65 mmol) in CH_2Cl_2 (40 mL), according to general procedure B, afforded after purification through silica gel chromatography (gradient, 10–20% ethyl acetate–petrol) the title compound *syn*-**3a** (1.451 g, 5.11 mmol) in 58% yield as a white solid, mp 131–133 °C; ν_{max} (KBr disc)/cm^{-1} 3510 (s, OH), 1773 (C=O)$_{ox}$, 1676 (C=O); δ_H(300 MHz, $CDCl_3$) 1.02 (3H, d, *J* 7.0, $CH(CH_3)_2$), 1.03 (3H, d, *J* 7.0, $CH(CH_3)_2$), 1.12–1.27 (4H, m, Cy–*H*), 1.61–1.67

(2H, m, Cy–*H*), 1.73–1.77 (2H, m, Cy–*H*), 1.83–1.91 (2H, m, Cy–*H*), 2.04–2.10 (1H, m, Cy–*H*), 2.31 (1H, m, *J* 7.0, 5.0, C*H*(CH$_3$)$_2$), 3.72–3.78 (1H, m, C*H*OH), 4.04 (2H, app t, *J* 8.0, C*H*$_2$N), 4.22 (1H, dd, *J* 7.0, 5.0, C*H*^{i}Pr), 4.41 (2H, app t, *J* 8.0, C*H*$_2$O); δ_C(CDCl$_3$) 19.6, 21.5, 26.7, 27.4, 28.2, 30.6, 41.7, 43.0, 49.3, 61.9, 76.0, 153.7, 175.6; *m/z* (FAB$^+$) 284 (97, MH$^+$), 266 (100%, M$^+$–OH); HRMS (FAB$^+$) $C_{15}H_{26}NO_4$ [MH$^+$] requires 284.1862; found 284.1868.

***syn*-3-(3-Hydroxy-2-methyl-3-phenylpropanoyl)-1,3-oxazolidin-2-one 3b**[27]. Reaction of 3-propionyl-1,3-oxazolidin-2-one **2a** (0.545 g, 3.81 mmol) with a 0.5 M solution of 9-BBN-OTf in hexanes (9.14 mL, 4.57 mmol), *N*,*N*-diisopropylethylamine (0.86 mL, 4.95 mmol) and benzaldehyde (0.43 mL, 4.19 mmol) in CH_2Cl_2 (20 mL), according to general procedure B, afforded after purification through silica gel chromatography (gradient, 20–30% ethyl acetate–petrol) the title compound ***syn*-3b** (0.653 g, 2.62 mmol) in 69% yield as a white crystalline solid, mp 102–104 °C (lit,[27] 105–106 °C); ν_{max} (KBr disc)/cm^{-1} 3561 (s, OH), 1766 (C=O)$_{ox}$, 1682 (C=O); δ_H(300 MHz, CDCl$_3$) 1.15 (3H, d, *J* 7.0, C*H*$_3$), 3.07 (1H, d, *J* 3.0, O*H*), 3.95–4.07 (2H, m, C*H*$_2$N), 4.12 (1H, qd, *J* 7.0, 3.0, CHC*H*$_3$), 4.31–4.45 (2H, m, C*H*$_2$O), 5.13 (1H, app t, *J* 3.0, C*H*OH), 7.24–7.43 (5H, m, Ar–*H*); δ_C(CDCl$_3$) 10.8, 43.0, 44.6, 62.4, 73.9, 126.4, 127.9, 128.6, 141.6, 153.5, 177.2; *m/z* (CI$^+$, NH$_3$) 267 (41, MNH$_4^+$), 250 (10, MH$^+$), 232 (38, M$^+$–OH), 206 (22, MH$^+$–CO$_2$), 161 (100%); HRMS (FAB$^+$) $C_{13}H_{16}NO_4$ [MH$^+$] requires 250.1079; found 250.1081.

***syn*-3-(3-Hydroxy-2-methylpentanoyl)-1,3-oxazolidin-2-one 3c.** Reaction of 3-propionyl-1,3-oxazolidin-2-one **2a** (0.991 g, 6.93 mmol) with a 1.0 M solution of 9-BBN-OTf in CH_2Cl_2 (8.39 mL, 8.39 mmol), *N*,*N*-diisopropylethylamine (1.70 mL, 9.79 mmol) and propionaldehyde (0.56 mL, 7.69 mmol) in CH_2Cl_2 (35 mL), according to general procedure B, afforded after purification through silica gel chromatography (gradient, 25–40% ethyl acetate–petrol) the title compound ***syn*-3c** (0.427 g, 2.12 mmol) in 31% yield as a white solid, mp 60–62 °C; $C_9H_{15}NO_4$ requires C, 53.7; H, 7.51; N, 6.96%; found C, 53.6; H, 7.45; N, 6.89%; ν_{max}(KBr disc)/cm^{-1} 3471 (br, OH), 1752 (C=O)$_{ox}$, 1696 (C=O); δ_H(300 MHz, CDCl$_3$) 0.91 (3H, t, *J* 7.5, CH$_2$C*H*$_3$), 1.13 (3H, d, *J* 7.0, C*H*C*H*$_3$), 1.44 (2H, m, C*H*$_2$CH$_3$), 2.78 (1H, br s, O*H*), 3.79–3.89 (2H, m, C*H*OH, C*H*CH$_3$), 4.01–4.07 (2H, m, C*H*$_2$N), 4.37 (2H, app t, *J* 8.5, C*H*$_2$O); δ_C(CDCl$_3$) 8.3, 8.5, 24.8, 39.6, 40.8, 60.1, 71.2, 151.4, 175.6; *m/z* (CI$^+$, iso-butane) 202 (100, MH$^+$), 184 (95, M$^+$–OH), 143 (57%, M$^+$–CH$_3$CH$_2$CHOH); HRMS (FAB$^+$) $C_9H_{16}NO_4$ [MH$^+$] requires 202.1079; found 202.1080.

***syn*-3-(2-Benzyl-3-hydroxydecanoyl)-1,3-oxazolidin-2-one 3d.** Reaction of 3-(3-phenylpropanoyl)-1,3-oxazolidin-2-one **2c** (0.500 g, 2.28 mmol) with a 0.5 M solution of 9-BBN-OTf in hexanes (5.48 mL, 2.74 mmol), *N*,*N*-diisopropylethylamine (0.56 mL, 3.20 mmol) and octanal (0.39 mL, 2.51 mmol) in CH_2Cl_2 (10 mL), according to general procedure B, afforded after purification through silica gel chromatography (20% ethyl acetate–petrol) the title compound ***syn*-3d** (0.582 g, 1.68 mmol) in 74% yield as a colourless oil, ν_{max}(neat)/cm^{-1} 3474 (br, OH), 1775 (C=O)$_{ox}$, 1695 (C=O); δ_H(300 MHz, CDCl$_3$) 0.81 (3H, t, *J* 7.0, C*H*$_3$), 1.16–1.28 (8H, m, C*H*$_2$), 1.44–1.52 (4H, m, C*H*$_2$), 2.65 (1H, br s, O*H*), 2.92 (1H, dd, *J* 13.0, 5.5, CH$_A$H$_B$Ph), 2.99 (1H, dd, *J* 13.0, 10.0, CH$_A$*H*$_B$Ph), 3.62 (1H, ddd, *J* 10.0, 9.0, 6.0, CH$_A$H$_B$N), 3.73–4.00 (3H, m, CH$_A$*H*$_B$N, C*H*OH, CH$_A$H$_B$O), 4.18 (1H, app dt, *J* 9.0, 6.0, CH$_A$*H*$_B$O), 4.33–4.40 (1H, m, C*H*CH$_2$Ph), 7.11–7.19 (5H, m, Ar–*H*); δ_C(CDCl$_3$) 14.5, 23.0, 26.4, 29.6, 29.9, 32.2, 33.5, 34.4, 42.9, 49.5, 62.1, 72.6, 126.8, 128.7, 129.4, 139.3, 153.7, 175.9; *m/z* (CI$^+$, NH$_3$) 365 (11, MNH$_4^+$), 348 (13, MH$^+$), 237.2 (100%); HRMS (ES$^+$) $C_{20}H_{30}NO_4$ [MH$^+$] requires 348.2169; found 348.2171.

***syn*-3-(3-Hydroxy-2-isopropylpentanoyl)-1,3-oxazolidin-2-one 3e**[41]. Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one **2b** (0.965 mg, 5.85 mmol) with a 0.5 M solution of 9-BBN-OTf in CH_2Cl_2 (14.0 mL, 7.02 mmol), *N*,*N*-diisopropylethylamine (1.43 mL, 8.19 mmol) and propionaldehyde (0.47 mL, 6.44 mmol) in CH_2Cl_2 (30 mL), according to general procedure B, afforded after purification through silica gel chromatography (gradient, 25–40% ethyl acetate–petrol) the title compound ***syn*-3e** (0.644 g, 2.81 mmol) in 48% yield as a white solid, mp 60–62 °C; ν_{max}(KBr disc)/cm^{-1} 3463 (br, OH), 1752 (C=O)$_{ox}$, 1696 (C=O); δ_H(300 MHz, CDCl$_3$) 0.85 (3H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 0.90 (3H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 0.91 (3H, t, *J* 7.0, CH$_2$C*H*$_3$), 1.35 (1H, ddq, *J* 14.0, 10.0, 7.0, CH$_A$H$_B$CH$_3$), 1.51 (1H, dqd, *J* 14.0, 7.0, 2.3, CH$_A$*H*$_B$CH$_3$), 2.12 (1H, m, *J* 8.0, 7.0, C*H*(CH$_3$)$_2$), 2.54 (1H, br s, OH), 3.83 (1H, app t, *J* 7.0, C*H*^{i}Pr), 3.91–4.02 (3H, m, C*H*$_2$N, C*H*OH), 4.30–4.37 (2H, m, C*H*$_2$O); δ_C(CDCl$_3$) 9.7, 19.2, 19.9, 24.4, 27.0, 41.8, 53.1, 60.8, 72.1, 153.3, 173.6; *m/z* (CI$^+$, iso-butane) 230 (5, MH$^+$), 212 (8, M$^+$–OH), 171 (34%, M$^+$–CH$_3$CH$_2$CHOH); HRMS (FAB$^+$) $C_{11}H_{20}NO_4$ [MH$^+$] requires 230.1392; found 230.1394.

***syn*-3-{2-[Hydroxy(phenyl)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one 3f.** Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one **2b** (0.993 g, 5.81 mmol) with a 0.5 M solution of 9-BBN-OTf in hexanes (11.7 mL, 5.85 mmol), *N*,*N*-diisopropylethylamine (1.40 mL, 8.19 mmol) and benzaldehyde (0.65 mL, 6.43 mmol) in CH_2Cl_2 (30 mL), according to general procedure B, afforded after purification through silica gel chromatography (25% ethyl acetate–petrol) the title compound ***syn*-3f** (0.811 g, 2.93 mmol) in 50% yield as a white solid, mp 93–95 °C; ν_{max}(KBr disc)/cm^{-1} 3450 (s, OH), 1751 (C=O)$_{ox}$, 1695 (C=O); δ_H(300 MHz, CDCl$_3$) 1.01 (3H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 1.08 (3H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 2.36 (1H, m, *J* 7.0, 5.5, C*H*(CH$_3$)$_2$), 2.41 (1H, d, *J* 3.0, O*H*), 3.62 (1H, ddd, *J* 11.0, 9.5, 7.0, CH$_A$H$_B$N), 3.84 (1H, ddd, *J* 11.0, 9.5, 7.0, CH$_A$*H*$_B$N), 4.07 (1H, app dt, *J* 9.0, 8.0, CH$_A$H$_B$O), 4.24 (1H, app dt, *J* 9.0, 8.0, CH$_A$*H*$_B$O), 4.48 (1H, dd, *J* 8.0, 5.5, C*H*^{i}Pr), 5.01 (1H, dd, *J* 8.0, 3.0, C*H*OH), 7.25–7.40 (5H, m, Ar–*H*); δ_C(CDCl$_3$) 18.0, 19.8, 27.1, 41.3, 53.0, 60.3, 72.9, 125.6, 126.7, 127.1, 140.9, 152.0, 172.7; *m/z* (CI$^+$, NH$_3$) 295 (8, MNH$_4^+$), 278 (5, MH$^+$), 260 (28, M$^+$–OH), 234 (9, M$^+$-^{i}Pr), 105 (100%); HRMS (ES$^+$) $C_{15}H_{23}N_2O_4$ [MNH$_4^+$] requires 295.1652; found 295.1653.

***syn*-3-{2-[Hydroxy(4-methoxyphenyl)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one 3g.** Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one **2b** (1.500 g, 8.77 mmol) with a 0.5 M solution of 9-BBN-OTf in hexanes (21.10 mL, 10.53 mmol), *N*,*N*-diisopropylethylamine (1.99 mL, 11.40 mmol) and *p*-anisaldehyde (1.17 mL, 9.65 mmol) in CH_2Cl_2 (40 mL), according to general procedure B, afforded after purification through silica gel chromatography (gradient, 10–20% ethyl acetate–petrol) the title compound ***syn*-3g** (1.592 g, 5.18 mmol) in 60% yield as a white crystalline solid, mp 117–118 °C; ν_{max} (KBr disc)/cm^{-1} 3449 (s, OH), 1755 (C=O)$_{ox}$, 1691 (C=O); δ_H(300 MHz, CDCl$_3$) 1.02 (3H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 1.08 (3H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 2.24 (1H, d, *J* 3.5, O*H*), 2.35 (1H, m, *J* 7.0, 5.5, C*H*(CH$_3$)$_2$), 3.65 (1H, ddd, *J* 11.0, 9.5, 7.0, CH$_A$H$_B$N), 3.79 (3H, s, ArOC*H*$_3$), 3.86 (1H, ddd, *J* 11.0, 9.5, 7.0, CH$_A$*H*$_B$N), 4.12 (1H, app dt, *J* 9.0, 7.0, CH$_A$H$_B$O), 4.26 (1H, app td, *J* 9.0, 7.0, CH$_A$*H*$_B$O), 4.48 (1H, dd, *J* 8.0, 5.5, C*H*^{i}Pr), 4.97 (1H, dd, *J* 8.0, 3.5, C*H*OH), 6.84 (2H, d, *J* 8.5, Ar–*H*), 7.30 (2H, d, *J* 8.5, Ar–*H*); δ_C(CDCl$_3$) 19.5, 21.3, 28.7, 42.9, 54.5, 55.6, 61.8, 74.0, 114.0, 128.5, 134.6, 153.6, 159.6, 174.2; *m/z* (EI$^{+\bullet}$) 307 (12, M$^{+\bullet}$), 171 (28, M$^{+\bullet}$–ArCHOH$^\bullet$), 149 (100%); HRMS (FAB$^+$) $C_{16}H_{21}NO_5$ [MH$^+$] requires 307.1420; found 307.1426.

***syn*-3-(3-Hydroxy-2-phenylpentanoyl)-1,3-oxazolidin-2-one 3h.** Reaction of 3-(2-phenylacetyl)-1,3-oxazolidin-2-one **2d** (0.994 g, 4.85 mmol) with a 1.0 M solution of 9-BBN-OTf in CH_2Cl_2 (5.86 mL, 5.86 mmol), *N*,*N*-diisopropylethylamine (1.20 mL, 6.83 mmol) and propionaldehyde (0.39 mL, 5.37 mmol) in CH_2Cl_2 (20 mL), according to general procedure B, afforded after purification through silica gel chromatography

(25% ethyl acetate–petrol) the title compound *syn*-**3h** (0.464 g, 1.76 mmol) in 37% yield as a colourless oil, ν_{max}(neat)/cm^{-1} 3519 (br, OH), 1771 (C=O)$_{ox}$, 1694 (C=O); δ_H(300 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.5, CH_2CH_3), 1.35–1.48 (2H, m, CH_2CH_3), 2.70 (1H, d, *J* 3.0, O*H*), 3.92 (1H, ddd, *J* 11.0, 9.5, 6.5, CH_AH_BN), 4.06 (1H, ddd, *J* 11.0, 9.5, 7.0, CH_AH_BN), 4.11–4.17 (1H, m, C*H*OH), 4.29 (1H, app dt, *J* 9.5, 8.0, CH_AH_BO), 4.38 (1H, app dt, *J* 9.5, 8.0, CH_AH_BO), 5.04 (1H, d, *J* 5.5, C*H*Ph), 7.26–7.44 (5H, m, Ar–H); δ_C($CDCl_3$) 10.5, 27.6, 42.9, 53.5, 62.0, 74.0, 128.1, 128.7, 130.3, 134.2, 153.0, 174.2; *m*/*z* (CI$^+$, NH_3) 281 (20, MNH_4^+), 264 (19, MH^+), 223 (100%); HRMS (ES$^+$) $C_{14}H_{18}NO_4$ [MH^+] requires 264.1230, found 264.1227.

***syn*-3-[(*E*)-3-Hydroxy-2-isopropyl-4-hexenoyl]-1,3-oxazolidin-2-one 3i.** Reaction of 3-(3-methylbutanoyl)-1,3-oxazolidin-2-one **2b** (0.965 g, 5.85 mmol) with a 0.5 M solution of 9-BBN-OTf in hexanes (14.10 mL, 7.02 mmol), *N*,*N*-diisopropylethylamine (1.32 mL, 7.60 mmol) and *trans*-crotonaldehyde (0.53 mL, 6.44 mmol) in CH_2Cl_2 (30 mL), according to general procedure B, afforded after purification through silica gel chromatography (25% ethyl acetate–petrol) the title compound *syn*-**3i** (1.090 g, 4.54 mmol) in 72% yield as a low-melting point white solid, ν_{max}(nujol)/cm^{-1} 3454 (br, OH), 1770 (C=O)$_{ox}$, 1690 (C=O); δ_H(300 MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.5, $CH(CH_3)_2$), 0.97 (3H, d, *J* 6.5, $CH(CH_3)_2$), 1.72 (3H, d, *J* 5.5, $CH{=}CHCH_3$), 1.99–2.11 (1H, m, $CH(CH_3)_2$), 2.23 (1H, br s, O*H*), 4.01–4.10 (3H, m, CH_2N, C*H*^{i}Pr), 4.34–4.48 (3H, m, CH_2O, C*H*OH), 5.60–5.81 (2H, m, $CH{=}CHCH_3$); δ_C($CDCl_3$) 18.2, 20.4, 21.1, 28.6, 43.2, 54.3, 62.0, 73.5, 130.0, 130.5, 154.7, 174.7; *m*/*z* (CI$^+$, iso-butane) 242 (6, MH^+), 224.1 (75, M^+–OH), 171.0 (64, M^+–$CHOHCHCHCH_3$), 156.0 (100%); HRMS (FAB$^+$) $C_{12}H_{20}NO_4$ [MH^+] requires 242.1392; found 242.1393.

***syn*-3-[(*E*)-3-Hydroxy-2-methyl-5-phenyl-4-pentenoyl]-1,3-oxazolidin-2-one 3j.** Reaction of 3-propionyl-1,3-oxazolidin-2-one **2a** (0.500 g, 3.50 mmol) with a 0.5 M solution of 9-BBN-OTf in hexanes (8.40 mL, 4.20 mmol), *N*,*N*-diisopropylethylamine (0.79 mL, 4.55 mmol) and *trans*-cinnamaldehyde (0.49 mL, 3.85 mmol) in CH_2Cl_2 (15 mL), according to general procedure B, afforded after purification through silica gel chromatography (gradient, 20–40% EtOAc–petrol) the title compound *syn*-**3j** (0.841 g, 3.06 mmol) in 88% yield as a white crystalline solid, mp 100–101 °C; ν_{max}(KBr disc)/cm^{-1} 3476 (s, OH), 1762 (C=O)$_{ox}$, 1683 (C=O); δ_H(300 MHz, $CDCl_3$) 1.17 (3H, d, *J* 7.0, CH_3), 2.97 (1H, d, *J* 1.0, O*H*), 3.88–3.99 (3H, m, CH_2N, $CHCH_3$), 4.28–4.34 (2H, m, CH_2O), 4.58 (1H, ddd, *J* 6.0, 4.0, 1.0, C*H*OH), 6.14 (1H, dd, *J* 16.0, 6.0, *H*C=CHPh), 6.59 (1H, d, *J* 16.0, HC=C*H*Ph), 7.15–7.34 (5H, m, Ar–*H*); δ_C($CDCl_3$) 11.6, 43.0, 43.5, 62.4, 73.2, 126.9, 128.1, 129.0 (2C), 131.8, 136.9, 153.8, 176.8; *m*/*z* (EI$^{+\bullet}$) 275 (7, $M^{+\bullet}$), 143 (42, $M^{+\bullet}$–$PhCHCHCHOH^\bullet$), 104.1 (100%); HRMS (ES$^+$) $C_{15}H_{21}N_2O_4$ [MNH_4^+] requires 293.1496; found 293.1495.

(*E*)-3-Cyclohexyl-*N*-(2-hydroxyethyl)-2-isopropyl-2-propenamide 4a. Reaction of *syn*-3-{2-[cyclohexyl(hydroxy)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one **3a** (0.100 g, 0.35 mmol) with a 0.5 M solution of KHMDS in toluene (1.06 mL, 0.53 mmol) in THF (2 mL), according to general procedure C, gave the title compound (*E*)-**4a** (0.075 g, 0.31 mmol) in 94% de. The crude product was purified for analysis by silica gel chromatography (gradient, 20–30% ethyl acetate–petrol), to afford the title compound (*E*)-**4a** (0.064 g, 0.27 mmol) in 77% yield and >95% de as a white solid, mp 84–86 °C; ν_{max}(KBr disc)/cm^{-1} 3291 (br, OH, NH), 1652 (C=O), 1619 (C=C), 1541 (C=O); δ_H(300 MHz, $CDCl_3$) 1.01–1.37 (6H, m, Cy-*H*), 1.18 (6H, d, *J* 7.0, $CH(CH_3)_2$), 1.60–1.78 (4H, m, Cy-*H*), 2.25–2.39 (1H, m, Cy-*H*), 2.83 (1H, m, *J* 7.0, $CH(CH_3)_2$), 2.95 (1H, t, *J* 4.5, O*H*), 3.44 (2H, app q, *J* 5.5, 4.5, CH_2NH), 3.74 (2H, app q, *J* 5.5, 4.5, CH_2OH), 5.59 (1H, d, *J* 10.0, C=C*H*), 6.08 (1H, br s, N*H*); δ_C($CDCl_3$) 22.1, 26.1, 26.2, 28.6, 33.3, 37.0, 42.9, 63.3, 137.9, 142.0, 173.1; *m*/*z* (EI$^{+\bullet}$) 239 (65, $M^{+\bullet}$), 224 (85, $M^{+\bullet}$–$CH_3^\bullet$), 179 (68%, $M^{+\bullet}$–$HOCH_2CH_2NH^\bullet$); HRMS (FAB$^+$) $C_{14}H_{25}NO_2$ [MH^+] requires 239.1885; found 239.1886.

X-Ray crystal data for 4a

($C_{14}H_{25}NO_2$): M_r = 239.35, *T* = 150(2) K, monoclinic, space group $P2_1/c$, *a* = 17.3540(2), *b* = 9.79700(10), *c* = 17.7370(2) Å, β = 104.153(1)°, *V* = 2924.06(7) Å^3, *Z* = 8, ρ_{calcd} = 1.087 Mg m^{-3}, μ = 0.071 mm^{-1}, λ = 0.71073 Å, θ_{max} = 27.46°, 43295 measured reflections, 6676 independent reflections [*R*(int) = 0.0787], GOF on F^2 = 1.007, R_1 = 0.0453, wR_2 = 0.1035 ($I>2\sigma(I)$), R_1 = 0.0818, wR_2 = 0.1198 (for all data), largest difference peak and hole 0.232 and −0.215 e Å^{-3}. Crystal data were collected on a Nonius Kappa CCD diffractometer. The structure was solved by direct methods and refined on all F^2 data using the SHELX-97 suite of programs.[44] The asymmetric unit was seen to consist of two molecules, one of which exhibited 55 : 45 positional disorder in the cyclohexyl carbons. All hydrogen atoms were included at calculated positions, with the exception of the H1 and H1A (hydroxyl groups), which were located and refined. The supramolecular array is dominated by extensive hydrogen-bonding.†

(*E*)-*N*-(2-Hydroxyethyl)-2-methyl-3-phenyl-2-propenamide 4b. Reaction of *syn*-3-(3-hydroxy-2-methyl-3-phenylpropanoyl)-1,3-oxazolidin-2-one **3b** (0.200 g, 0.80 mmol) with a 0.5 M solution of KHMDS in toluene (2.41 mL, 1.20 mmol) in THF (4 mL), according to general procedure C, afforded the title compound (*E*)-**4b** (0.143 g, 0.70 mmol) in 91% yield and >95% de as a white solid, mp 101–103 °C; ν_{max} (KBr disc)/cm^{-1} 3284 (br, OH, NH), 1644 (C=O), 1620 (C=C), 1575 (C=O); δ_H(300 MHz, $CDCl_3$) 2.04 (3H, d, *J* 1.0, C=C(CH_3)), 3.08 (1H, br s, O*H*), 3.46–3.51 (2H, m, CH_2N), 3.74 (2H, app t, *J* 5.0, CH_2O), 6.48 (1H, br s, N*H*), 7.19 (1H, s, C=C*H*), 7.20–7.33 (5H, m, Ar–H); δ_C($CDCl_3$) 14.6, 43.3, 62.8, 128.3, 128.7, 129.7, 131.7, 135.0, 136.3, 171.2; *m*/*z* (CI$^+$, NH_3) 206 (100%, MH^+); HRMS (FAB$^+$) $C_{12}H_{16}NO_2$ [MH^+] requires 206.1176, found 206.1177.

(*E*)-*N*-(2-Hydroxyethyl)-2-methyl-2-pentenamide 4c. Reaction of *syn*-3-(3-hydroxy-2-methylpentanoyl)-1,3-oxazolidin-2-one **3c** (0.050 g, 0.25 mmol) with a 0.5 M solution of KHMDS in toluene (0.75 mL, 0.37 mmol) in THF (3 mL), according to general procedure C, afforded the title compound (*E*)-**4c** (0.026 g, 0.17 mmol) in 67% yield and >95% de as a white solid of low melting point (<30 °C), ν_{max}(KBr disc)/cm^{-1} 3405 (br, OH, NH), 1701 (C=O), 1615 (C=C), 1538 (C=O); δ_H(300 MHz, $CDCl_3$) 1.04 (3H, t, *J* 7.5, CH_2CH_3), 1.85 (3H, s, CH_3), 2.17 (2H, app pentet, *J* 7.5, CH_2CH_3), 2.86 (1H, br s, O*H*), 3.50 (2H, app q, *J* 6.0, 5.0, CH_2NH), 3.77 (2H, app t, *J* 6.0, CH_2OH), 6.19 (1H, s, N*H*), 6.38 (1H, t, *J* 7.5, C=C*H*); δ_C($CDCl_3$) 11.5, 12.2, 20.6, 41.7, 61.4, 128.7, 137.5, 169.7; *m*/*z* (CI$^+$, NH_3) 158 (100%, MH^+); HRMS (ES$^+$) $C_8H_{16}NO_2$ [MH^+] requires 158.1176; found 158.1179.

(*E*)-2-Benzyl-*N*-(2-hydroxyethyl)-2-decenamide 4d. Reaction of *syn*-3-(2-benzyl-3-hydroxydecanoyl)-1,3-oxazolidin-2-one **3d** (0.135 g, 0.39 mmol) with a 0.5 M solution of KHMDS in toluene (1.17 mL, 0.58 mmol) in THF (3 mL), according to general procedure C, gave the title compound (*E*)-**4d** (0.110 g, 0.36 mmol) in 92% de. The crude product was purified for analysis by silica gel chromatography (60% ethyl acetate–petrol) to afford the title compound (*E*)-**4d** (0.108 g, 0.36 mmol) in 91% yield and >95% de as a colourless oil, ν_{max}(neat)/cm^{-1} 3342 (br, OH, NH), 1656 (C=O), 1620 (C=C), 1537 (C=O); δ_H(300 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.0, CH_3), 1.23–1.28 (8H, m, Alk-*H*), 1.39–1.46 (2H, m, CH_2), 2.21 (2H, app q, *J* 7.5, $CH{=}CCH_2$), 2.97 (1H, br s, O*H*), 3.33 (2H, app q, *J* 5.5, 5.0, CH_2NH), 3.57 (2H, m, CH_2OH), 3.69 (2H, s, CH_2Ph), 6.17

†CCDC reference number 207151. See http://dx.doi.org/10.1039/b503633j for crystallographic data in CIF or other electronic format.

(1H, br t, *J* 5.0, N*H*), 6.54 (1H, t, *J* 7.5, C=C*H*), 7.16–7.30 (5H, m, Ar–*H*); δ_C($CDCl_3$) 14.5, 23.0, 28.9, 29.3, 29.5, 29.8, 32.1, 33.1, 43.1, 62.9, 126.8, 128.5, 129.1, 134.0, 139.0, 139.3, 170.5; *m/z* (EI$^{+\bullet}$) 303 (10, M$^{+\bullet}$), 243 (13, M$^{+\bullet}$–$HOCH_2CH_2NH^{\bullet}$), 91 (100%, $PhCH_2^+$); HRMS (ES$^+$) $C_{19}H_{30}NO_2$ [MH$^+$] requires 304.2271; found 304.2275.

(*E*)-*N*-(2-Hydroxyethyl)-2-isopropyl-2-pentenamide 4e[45]. Reaction of *syn*-3-(3-hydroxy-2-methylpentanoyl)-1,3-oxazolidin-2-one **3e** (0.100 g, 0.44 mmol) with a 0.5 M solution of KHMDS in toluene (1.30 mL, 0.65 mmol) in THF (3 mL), according to general procedure C, afforded the title compound (*E*)-**4e** (0.080 g, 0.43 mmol) in 99% yield and >95% de as a colourless oil, ν_{max}(neat)/cm^{-1} 3338 (br, OH, NH), 1653 (C=O), 1617 (C=C), 1534 (C=O); δ_H(300 MHz, $CDCl_3$) 1.03 (3H, t, *J* 7.5, CH_2CH_3), 1.16 (6H, d, *J* 7.0, $CH(CH_3)_2$), 2.14 (2H, app pentet, *J* 7.5, CH_2CH_3), 2.81 (1H, septet, *J* 7.0, $CH(CH_3)_2$), 3.43 (2H, app q, *J* 5.5, 4.5, CH_2NH), 3.50 (1H, br s, O*H*), 3.73 (2H, app t, *J* 5.0, CH_2OH), 5.77 (1H, t, *J* 7.5, C=C*H*), 6.26 (1H, br s, N*H*); δ_C($CDCl_3$) 13.2, 20.1, 20.7, 27.2, 41.7, 61.8, 133.0, 142.2, 171.9; *m/z* (CI$^+$, iso-butane) 186 (88, MH$^+$), 185 (32, M$^+$), 125 (100%, M$^+$–$HOCH_2CH_2NH$); HRMS (FAB$^+$) $C_{10}H_{20}NO_2$ [MH$^+$] requires 186.1494, found 186.1495.

(*E*)-*N*-(2-Hydroxyethyl)-2-isopropyl-3-phenyl-2-propenamide 4f. Reaction of *syn*-3-{2-[hydroxy(phenyl)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one **3f** (0.085 g, 0.31 mmol) with a 0.5 M solution of KHMDS in toluene (1.08 mL, 0.54 mmol) in THF (3 mL), according to general procedure C, afforded title compound (*E*)-**4f** (0.068 g, 0.29 mmol) in 92% de. The crude product was purified for analysis by silica gel chromatography (40% ethyl acetate–petrol) to afford the title compound (*E*)-**4f** (0.065 g, 0.22 mmol) in 90% yield and >95% de as a white solid, mp 101–103 °C; ν_{max} (KBr disc)/cm^{-1} 3317 (s, OH, NH), 1641 (C=O), 1612 (C=C), 1538 (C=O); δ_H(300 MHz, $CDCl_3$) 1.24 (6H, d, *J* 7.0, $CH(CH_3)_2$), 2.95 (1H, br s, O*H*), 3.07 (1H, septet, *J* 7.0, $CH(CH_3)_2$), 3.52 (2H, app q, *J* 5.5, 5.0, CH_2NH), 3.79 (2H, app t, *J* 5.0, CH_2OH), 6.33 (1H, br s, N*H*), 6.79 (1H, br s, C=C*H*), 7.25–7.39 (5H, m, Ar–*H*); δ_C($CDCl_3$) 21.9, 28.5, 42.8, 63.0, 128.0, 128.8, 129.1, 130.1, 136.1, 145.7, 172.4; *m/z* (EI$^{+\bullet}$) 233 (19, M$^{+\bullet}$), 173 (48, M$^{+\bullet}$–$HOCH_2CH_2NH^{\bullet}$), 145(57, M$^{+\bullet}$–$HOCH_2CH_2NHCO^{\bullet}$), 91 (100%, $PhCH_2^+$); HRMS (ES$^+$) $C_{14}H_{20}NO_2$ [MH$^+$] requires 234.1489, found 234.1489.

(*E*)-*N*-(2-Hydroxyethyl)-2-isopropyl-3-(4-methoxyphenyl)-2-propenamide 4g. Reaction of *syn*-3-{2-[hydroxy(4-methoxyphenyl)methyl]-3-methylbutanoyl}-1,3-oxazolidin-2-one **3g** (0.200 g, 0.65 mmol) with a 1.0 M solution of KHMDS in toluene (1.95 mL, 0.98 mmol) in THF (4 mL), according to general procedure C, gave the title compound (*E*)-**4g** (0.155 g, 0.59 mmol) in 90% de. The crude product was purified for analysis by silica gel chromatography (40% ethyl acetate–petrol) to afford the title compound (*E*)-**4g** (0.149 g, 0.57 mmol) in 88% yield and >95% de as a white solid, mp 91–93 °C; ν_{max} (KBr disc)/cm^{-1} 3279 (s, OH), 3064 $(C=C)_{ar}$, 2834 $(C–H)_{OMe}$, 1645 (C=O), 1620 (C=C), 1606 $(C=C)_{ar}$, 1542 (C=O), 1510 $(C=C)_{ar}$; δ_H(300 MHz, $CDCl_3$) 1.24 (6H, d, *J* 7.0, $CH(CH_3)_2$), 3.09 (1H, septet, *J* 7.0, $CH(CH_3)_2$), 3.18 (1H, br s, O*H*), 3.50 (2H, app dt, *J* 5.5, 5.0, CH_2NH), 3.75–3.85 (2H, m, CH_2OH), 3.82 (3H, s, $ArOCH_3$), 6.38 (1H, br s, N*H*), 6.73 (1H, s, C=C*H*), 6.89 (2H, d, *J* 9.0, Ar–*H*), 7.21 (2H, d, *J* 9.0, Ar–*H*); δ_C($CDCl_3$) 21.9, 28.4, 42.8, 55.7, 62.9, 114.2, 128.5, 129.7, 130.5, 144.1, 159.4, 172.6; *m/z* (EI$^{+\bullet}$) 263 (35, M$^{+\bullet}$), 203 (26, M$^{+\bullet}$–$HOCH_2CH_2NH^{\bullet}$), 84 (100%); HRMS (FAB$^+$) $C_{15}H_{21}NO_3$ [MH$^+$] requires 263.1521; found 263.1518.

(*E*)-*N*-(2-Hydroxyethyl)-2-phenyl-2-pentenamide 4h. Reaction of *syn*-3-(3-hydroxy-2-phenylpentanoyl)-1,3-oxazolidin-2-one **3h** (0.200 g, 0.76 mmol) with a 0.5 M solution of KHMDS in toluene (2.24 mL, 1.12 mmol) in THF (2 mL), according to general procedure C, gave a mixture of the title compound (*E*)-**4h** (80%) in >95% de and the parent *N*-acyl oxazolidin-2-one **2d** (20%). The crude product was purified by silica gel chromatography (40% ethyl acetate–petrol) to afford the title compound (*E*)-**4h** (0.078 g, 0.35 mmol) in 47% yield and >95% de as a colourless oil, ν_{max} (neat)/cm^{-1} 3418 (br, OH, NH), 1657 (C=O), 1617 (C=C), 1522 (C=O); δ_H(300 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.5, CH_2CH_3), 1.98 (2H, app pentet, *J* 7.5, CH_2CH_3), 3.16 (1H, br s, O*H*), 3.39 (2H, app q, *J* 5.5, 5.0, CH_2NH), 3.66 (2H, app t, *J* 5.0, CH_2OH), 5.79 (1H, br s, N*H*), 7.03 (1H, t, *J* 7.5, C=C*H*), 7.17–7.21 (2H, m, Ar–*H*), 7.35–7.46 (3H, m, Ar–*H*); δ_C($CDCl_3$) 13.4, 23.1, 43.4, 62.8, 128.6, 129.0, 130.2, 135.1, 135.8, 143.8, 168.8; *m/z* (EI$^{+\bullet}$) 219 (18, M$^{+\bullet}$), 159 (22, M$^{+\bullet}$–$HOCH_2CH_2NH^{\bullet}$), 77 (100%); HRMS (FAB$^+$) $C_{13}H_{18}NO_2$ [MH$^+$] requires 220.1332; found 220.1332.

(2*E*,4*E*)-*N*-(2-Hydroxyethyl)-2-isopropyl-2,4-hexadienamide 4i and (2*Z*,4*E*)-*N*-(2-hydroxyethyl)-2-isopropyl-2,4-hexadienamide 5. Reaction of *syn*-3-[(*E*)-3-hydroxy-2-isopropyl-4-hexenoyl]-1,3-oxazolidin-2-one **3i** (0.200 g, 0.83 mmol) with a 0.5 M solution of KHMDS in toluene (2.50 mL, 1.25 mmol) in THF (5 mL), according to general procedure C, gave the title compound (*E*,*E*)-**4i** (0.153 g, 0.78 mmol) in 93% yield and in 60% de which was purified through silica (pre-coated with silver nitrate) gel chromatography to afford the title compound (*E*,*E*)-**4i** (0.016 g, 0.08 mmol) in 10% yield as a pale oil, δ_H(300 MHz, $CDCl_3$) 1.20 (6H, d, *J* 7.0, $CH(CH_3)_2$), 1.83 (3H, dd, *J* 7.0, 1.5, $CH=CHCH_3$), 2.95 (1H, septet, *J* 7.0, $CH(CH_3)_2$), 3.20 (1H, br s, O*H*), 3.45 (2H, app dt, *J* 5.5, 4.0, CH_2NH), 3.74 (2H, app t, *J* 5.0, CH_2OH), 5.89 (1H, dq, *J* 13.0, 7.0, $CH=CHCH_3$), 6.21 (1H, br s, N*H*), 6.33 (1H, br d, *J* 10.5, $CH–CH=CHCH_3$), 6.39 (1H, ddq, *J* 13.0, 10.5, 1.5, $CH–CH=CHCH_3$); δ_C($CDCl_3$) 19.0, 21.8, 28.6, 42.8, 63.0, 126.6, 130.6, 135.2, 141.0, 172.5; *m/z* (EI$^{+\bullet}$) 197 (23, M$^{+\bullet}$), 182 (33, M$^{+\bullet}$–$CH_3^{\bullet}$), 169 (38, M$^{+\bullet}$–$CH_3CH^{\bullet}$), 154 (100, M$^{+\bullet}$–$(CH_3)_2CH^{\bullet}$), 137 (28, M$^{+\bullet}$–$HO(CH_2)_2NH^{\bullet}$), 109 (43, M$^{+\bullet}$–$HO(CH_2)_2NHCO^{\bullet}$), and its geometric isomer (*Z*,*E*)-**5** (0.015 g, 0.08 mmol) in 9% yield, δ_H(300 MHz, $CDCl_3$) 1.08 (6H, d, *J* 7.0, $CH(CH_3)_2$), 1.77 (3H, dd, *J* 7.0, 1.5, $CH=CHCH_3$), 2.64 (1H, septet, *J* 7.0, $CH(CH_3)_2$), 3.00 (1H, br s, O*H*), 3.53 (2H, app dt, *J* 5.5, 4.5, CH_2NH), 3.78 (2H, app t, *J* 5.0, CH_2OH), 5.79 (1H, dq, *J* 15.0, 7.0, $CHCH=CHCH_3$), 5.99 (1H, d, *J* 11.0, $CH–CH=CHCH_3$), 6.13 (1H, br s, N*H*), 6.28 (1H, ddq, *J* 15.0, 11.0, 1.5, $CH–CH=CHCH_3$).

(2*E*,4*E*)-*N*-(2-Hydroxyethyl)-2-methyl-5-phenyl-2,4-pentadienamide 4j. Reaction of *syn*-3-[(*E*)-3-hydroxy-2-methyl-5-phenyl-4-pentenoyl]-1,3-oxazolidin-2-one **4j** (0.275 g, 1.00 mmol) with a 0.5 M solution of KHMDS (3.00 mL, 1.50 mmol) in THF (5 mL), according to general procedure C, gave the title compound (*E*)-**4j** (0.223 g, 0.97 mmol) in 97% yield and in 60% de The crude product was purified for analysis by recrystallisation from hot ethyl acetate, to afford the title compound (*E*)-**4j** (0.147 g, 0.64 mmol) in 64% yield and >95% de as a white solid, mp 141–142 °C; ν_{max}(KBr disc)/cm^{-1} 3293 (br, OH), 3250 (br, NH), 1642 (C=O), 1585 (C=C), 1542 (C=O); δ_H(300 MHz, $CDCl_3$) 2.08 (3H, s, CH_3), 2.87 (1H, t, *J* 5.0, O*H*), 3.55 (2H, app q, *J* 5.5, 5.0, CH_2NH), 3.80 (2H, app q, *J* 5.0, 5.0, CH_2OH), 6.32 (1H, br s, N*H*), 6.83 (1H, d, *J* 15.0, $CH–CH=CHPh$), 7.01 (1H, d, *J* 11.0, $CHCH=CHPh$), 7.10 (1H, dd, *J* 15.0, 11.0, $CHCH=CHPh$), 7.28–7.48 (5H, m, Ar–*H*); δ_C($CDCl_3$) 13.6, 43.3, 63.1, 124.0, 127.3, 128.9, 129.1, 129.9, 134.9, 137.0, 138.6, 170.5; *m/z* (EI$^{+\bullet}$) 231 (33, M$^{+\bullet}$), 171 (80, MH$^{+\bullet}$–$HOCH_2CH_2NH^{\bullet}$), 154 (78, M$^{+\bullet}$–Ph$^{\bullet}$), 141 (47, M$^{+\bullet}$–PhCH$^{\bullet}$), 128 (100, M$^{+\bullet}$–PhCHCH$^{\bullet}$), 115 (38%, M$^{+\bullet}$–PhCHCHCH$^{\bullet}$); HRMS (FAB$^+$) $C_{14}H_{18}NO_2$ [MH$^+$] requires 232.1332, found 232.1330.

3-{(2*R*,3*R*)-3-Hydroxy-3-[(4*R*)-4-isopropenyl-1-cyclohexen-1-yl]-2-methylpropanoyl}-1,3-oxazo lid-in-2-one 8a and 3-{(2*S*,3*S*)-3-hydroxy-3-[(4*R*)-4-isopropenyl-1-cyclohexen-1-yl]-2-methylpropanoyl}-1,3-oxazolidin-2-one 9a. Reaction of 3-propionyl-1,3-oxazolidin-2-one **2a** (0.500 g, 3.50 mmol) with a 0.5 M

solution of 9-BBN-OTf in hexanes (8.40 mL, 4.20 mmol), *N*,*N*-diisopropylethylamine (0.85 mL, 4.90 mmol) and L-(−)-perillaldehyde (0.60 mL, 3.85 mmol) in CH_2Cl_2 (20 mL), according to general procedure B, afforded after purification through silica gel chromatography (20% ethyl acetate–petrol) the title compounds **8a/9a** (0.656 g, 2.24 mmol) in 64% yield as a white solid, as a 1 : 1 mixture of diastereomers, mp 87–88 °C; ν_{max}(KBr disc)/cm^{-1} 3495 (s, OH), 1769 (C=O)$_{ox}$, 1691 (C=O); δ_H(300 MHz, $CDCl_3$) 1.13 (3H, d, *J* 6.0, CH_3, **8a**), 1.15 (3H, d, *J* 6.0, CH_3, **9a**), 1.38–1.55 (2H, m, Cy-*H*), 1.74 (6H, s, 2 × $CH_3C{=}CH_2$), 1.82–1.88 (2H, m, Cy-*H*), 1.92–2.06 (4H, m, Cy-*H*), 2.11–2.24 (4H, m, Cy-*H*), 2.76 (1H, s, O*H*, **8a**), 2.78 (1H, s, O*H*, **9a**), 3.75 (1H, m, $CHCH_3$, **8a**), 3.96–4.00 (1H, m, $CHCH_3$, **9a**), 4.05 (4H, app t, *J* 8.0, CH_2N), 4.35–4.45 (2H, m, C*H*OH), 4.44 (4H, app t, *J* 8.0, CH_2O), 4.70–4.76 (4H, m, $CH_2{=}C$), 5.80–5.83 (2H, m, C*H*=C); δ_C($CDCl_3$) 10.2, 10.9, 21.2, 21.3, 25.7, 26.0, 26.5, 27.7, 27.8, 30.6, 30.9, 40.4, 40.8, 41.2, 41.7, 43.1, 62.4, 68.4, 74.3, 74.6, 109.0, 109.1, 122.4, 123.0, 136.2, 136.7, 149.9, 150.2, 153.6, 177.5, 177.6; *m*/*z* (CI$^+$, NH_3) 311 (9, MNH_4^+), 294 (15, MH^+), 276 (40, M^+–OH), 161 (100), 144 (39%, MH^+–CHOHCy); HRMS (FAB$^+$) $C_{16}H_{24}NO_4$ [MH^+] requires 294.1700; found 294.1695.

3-(2*R*,3*S*,5*S*)-3-Hydroxy-2,5,9-trimethyl-8-decenoyl)-1,3-oxazolidin-2-one 8b and 3-(2*S*,3*R*,5*S*)-3-hydroxy-2,5,9-trimethyl-8-decenoyl)-1,3-oxazolidin-2-one 9b. Reaction of 3-propionyl-1,3-oxazolidin-2-one **2a** (0.300 g, 2.10 mmol) with a 0.5 M solution of 9-BBN-OTf in hexanes (5.03 mL, 2.52 mmol), *N*,*N*-diisopropylethylamine (0.51 mL, 2.94 mmol) and (*S*)-citronellal (0.42 mL, 2.31 mmol) in CH_2Cl_2 (10 mL), according to general procedure B, afforded after purification through silica gel chromatography (gradient, 20–30% ethyl acetate–petrol) the title compounds **8b/9b** (0.576 g, 1.94 mmol) in 93% yield as a low viscosity colourless oil, as a 1 : 1 mixture of diastereoisomers, ν_{max}(neat)/cm^{-1} 3502 (br, OH), 1771 (C=O)$_{ox}$, 1695 (C=O); δ_H(300 MHz, $CDCl_3$) 0.92 (6H, app t, *J* 7.0, $CHCH_3$, **8b** + **9b**), 1.05–1.28 (4H, m, Alk-*H*), 1.20 (3H, d, *J* 7.0, O=CCHCH_3, **8b**), 1.21 (3H, d, *J* 7.0, O=CCHCH_3, **9b**), 1.30–1.48 (4H, m, Alk-*H*), 1.60 (6H, s, CH=C(CH_3)CH_3), 1.68 (6H, s, CH=C(CH_3)CH_3), 1.54–1.70 (2H, m, $CHCH_3$), 1.92–2.08 (4H, m, $CH_2CH{=}C(CH_3)_2$), 2.73 (1H, d, *J* 2.3, OH, **8b**), 2.80 (1H, d, *J* 3.0, O*H*, **9b**), 3.73–3.83 (2H, m, O=CC*H*CH_3), 4.00–4.11 (6H, m, C*H*OH, CH_2N), 4.44 (4H, app t, *J* 8.0, CH_2O), 5.10 (2H, t, *J* 7.0, C*H*=C(CH_3)$_2$); δ_C($CDCl_3$) 10.6, 11.0, 18.1, 19.3, 20.6, 25.7, 25.9, 26.0, 26.1 (2C), 29.3, 29.6, 36.9, 38.3, 41.4, 41.5, 42.2 (2C), 42.9, 43.0, 62.3, 68.4, 69.6, 69.8, 125.1, 131.6, 131.6, 153.6, 153.6, 177.9, 178.0; *m*/*z* (EI$^+$) 297.2 (11, $M^{+\cdot}$), 143 (100%); HRMS (ES$^+$) $C_{16}H_{28}NO_4$ [MH^+] requires 298.2013; found 298.2009.

(2*R*,3*R*)-3-{3-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-2-methylpropanoyl}-1,3-oxazol-idin-2-one 8c and (2*S*,3*S*)-3-{3-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-2-methylpropanoyl}-1,3-oxazolidin-2-one 9c. Reaction of 3-propionyl-1,3-oxazolidin-2-one **2a** (0.200 g, 1.40 mmol) with a 0.5 M solution of 9-BBN-OTf in CH_2Cl_2 (3.36 mL, 1.68 mmol), *N*,*N*-diisopropylethylamine (0.34 mL, 1.96 mmol) and (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (0.19 mL, 1.54 mmol) in hexanes (7 mL), according to general procedure B, afforded after purification through silica gel chromatography (gradient, 40–50% ethyl acetate–petrol) the title compounds **8c/9c** (0.222 g, 0.81 mmol) in 58% yield as a thick colourless oil, as a 2 : 1 mixture of diastereoisomers, ν_{max}(neat)/cm^{-1} 3447 (br, OH), 1771 (C=O)$_{ox}$, 1699 (C=O); δ_H(300 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.5, $CHCH_3$, **8c**), 1.34 (6H, s, CH_3), 1.38 (3H, d, *J* 6.5, $CHCH_3$, **9c**), 1.43 (6H, s, CH_3), 2.55 (1H, d, *J* 6.5, O*H*, **8c**), 3.11 (1H, d, *J* 3.0, O*H*, **9c**), 3.72–4.18 (10H, m, $CHCH_3$, C*H*OH, C*H*OH, 2 × CH_2O), 4.05 (4H, app t, *J* 7.5, CH_2N), 4.44 (4H, app t, *J* 7.5, CH_2O); δ_C($CDCl_3$) 11.2, 12.1, 25.6, 25.8, 26.8, 27.1, 39.5, 41.3, 43.1, 62.3, 62.4, 66.6, 67.8, 68.4, 72.0, 73.1, 75.6, 77.2, 109.8, 110.1, 153.2, 153.6, 175.6, 178.0; *m*/*z* (CI$^+$, NH_3) 291 (30%, MNH_4^+), 274 (46, MH^+), 256 (5, M^+–OH), 230 (20, MH^+–CO_2), 144 (13, MH^+–CHOHR), 105.0 (100%); HRMS (ES$^+$) $C_{12}H_{20}NO_6$ [MH^+] requires 274.1285, found 274.1282.

(*E*,*E*)-*N*-(2-Hydroxyethyl)-3-[(4*R*)-4-isopropenyl-1-cyclohexen-1-yl]-2-methyl-2-propenamide 10a. Reaction of the mixture of aldols **8a/9a** (0.100 g, 0.34 mmol) with a 0.5 M solution of KHMDS in toluene (2.05 mL, 1.02 mmol) in THF (4 mL), according to general procedure C, gave the title compound (*R*,*E*,*E*)-**10a** in 50% de. The crude mixture was purified by silica gel chromatography (60% ethyl acetate–petrol) to afford the title compound (*R*,*E*,*E*)-**10a** (0.043 mg, 0.17 mmol) in 51% isolated yield and >95% de as a white solid, $[\alpha]_D^{21}$ −72.2 (*c* 0.90, CH_2Cl_2); mp 67–69 °C; ν_{max}(KBr disc)/cm^{-1} 3300 (br, NH), 3292 (s, OH), 1634 (C=O), 1603 (C=C), 1538 (C=O); δ_H(300 MHz, $CDCl_3$) 1.35–1.48 (1H, m, Cy-*H*), 1.68 (3H, s, $CH_2{=}CHCH_3$), 1.75–1.84 (1H, m, Cy-*H*), 1.95 (3H, s, CH=CCH_3), 2.00–2.11 (2H, m, Cy-*H*), 2.16–2.24 (3H, m, Cy-*H*), 3.28 (1H, s, O*H*), 3.42 (2H, app q, *J* 5.0, CH_2NH), 3.68 (2H, app t, *J* 5.0, CH_2OH), 4.67 (2H, d, *J* 7.0, C=CH_2), 5.76 (1H, m, C=C*H*CH_3), 6.33 (1H, br s, N*H*), 6.66 (1H, s, $CH_3C{=}CH$); δ_C($CDCl_3$) 14.7, 21.2, 28.0, 29.4, 31.6, 40.8, 43.3, 62.9, 109.3, 128.5, 131.5, 134.6, 137.4, 149.7, 171.8; *m*/*z* (EI$^{+\cdot}$) 249 (16, $M^{+\cdot}$), 208 (11, $M^{+\cdot}$–$CH_3CH(CH_2)^{\cdot}$), 189 (10%, $M^{+\cdot}$–$HOCH_2CH_2NH^{\cdot}$), 121 (55%, Cy^+), 91 (100%); HRMS (ES$^+$) $C_{15}H_{24}NO_2$ [MH^+] requires 250.1802, found 250.1802.

(2*E*,5*S*)-*N*-(2-Hydroxyethyl)-2,5,9-trimethyl-2,8-decadienamide 10b. Reaction of aldols **8b/9b** (0.150 mg, 0.51 mmol) with a 0.5 M solution of KHMDS in toluene (1.52 mL, 0.76 mmol) in THF (3 mL), according to general procedure C, gave the title compound (*S*,*E*)-**10b** (0.121 mg, 0.48 mmol) in 60% de. The crude product was purified by silica gel chromatography (60% ethyl acetate–petrol) to afford the title compound (*S*,*E*)-**10b** (0.071 g, 0.28 mmol) in 55% yield and >95% de as a colourless oil, $[\alpha]_D^{21}$ +2.7 (*c* 2.61, CH_2Cl_2), ν_{max}(neat)/cm^{-1} 3402 (br, OH, NH), 1657 (C=O), 1615 (C=C), 1538 (C=O); δ_H(300 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.5, $CHCH_3$), 1.12–1.27 (1H, m, $CH_AH_BCH_2CH{=}C(CH_3)_2$), 1.30–1.42 (1H, m, $CH_AH_BCH_2CH{=}C(CH_3)_2$), 1.55–1.65 (1H, m, $CHCH_3$), 1.60 (3H, s, CH=C(CH_3)$_2$), 1.68 (3H, s, CH=C(CH_3)$_2$), 1.85 (3H, s, CH=CCH_3), 1.90–2.05 (2H, m, $CH_2CH{=}C(CH_3)_2$), 2.10–2.19 (2H, m, $CH_2CH{=}CCH_3$), 3.48 (2H, app q, *J* 5.5, 5.0, CH_2NH), 3.61 (1H, br s, O*H*), 3.72–3.76 (2H, m, CH_2OH), 5.07 (1H, t, *J* 7.0, C*H*=C(CH_3)$_2$), 6.41 (1H, br s, N*H*), 6.44 (1H, t, *J* 6.5, C*H*=C); δ_C($CDCl_3$) 13.2, 18.1, 20.0, 26.0, 26.1, 33.1, 36.1, 37.2, 43.1, 62.8, 124.9, 131.1, 131.8, 136.6, 171.0; *m*/*z* (EI$^+$) 253 (46, $M^{+\cdot}$), 238 (18, $M^{+\cdot}$–$CH_3^{\cdot}$), 193 (5, $M^{+\cdot}$–$HOCH_2CH_2NH^{\cdot}$), 170 (41, $M^{+\cdot}$–$(CH_3)_2C{=}CHCH_2CH_2^{\cdot}$), 109 (100%); HRMS (ES$^+$) $C_{15}H_{28}NO_2$ [MH^+] requires 254.2115; found 254.2112.

(*E*)-3-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-*N*-(2-hydroxyethyl)-2-methyl-2-propenamide 10c. Reaction of aldols **8c/9c** (0.100 g, 0.37 mmol) with a 0.5 M solution of KHMDS (1.10 mL, 0.55 mmol) in THF (2 mL), according to general procedure C, gave the title compound (*S*,*E*)-**10c** in 80% de. The crude mixture was purified by silica gel chromatography (70% ethyl acetate–petrol) to afford the title compound (*S*,*E*)-**10c** (0.035 g, 0.15 mmol) in 42% yield and >95% de as a colourless oil, $[\alpha]_D^{21}$ +4.5 (*c* 1.54, CH_2Cl_2); ν_{max}(neat)/cm^{-1} 3305 (br, OH, NH), 1668 (C=O), 1622 (C=C), 1538 (C=O); δ_H(300 MHz, $CDCl_3$) 1.41 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.93 (3H, d, *J* 1.2, C=C(CH_3)), 3.27 (1H, s, O*H*), 3.47 (2H, app q, *J* 5.0, CH_2NH), 3.61 (1H, app t, *J* 8.0, CH_AH_BO), 3.74 (2H, app t, *J* 5.0, CH_2OH), 4.15 (1H, dd, *J* 8.0, 6.0, CH_AH_BO), 4.84 (1H, td, *J* 8.0, 6.0, C*H*OCH=), 6.25 (1H, dq, *J* 8.0, 1.2, C*H*=C), 6.52 (1H, br s, N*H*); δ_C($CDCl_3$) 13.8, 26.2, 27.0, 43.0, 62.3, 69.2, 72.9, 110.1, 132.8, 135.1, 170.1; *m*/*z* (CI$^+$, iso-butane) 230 (98, MH^+), 214 (20, M^+–$CH_3^{\cdot}$), 172 (68, M^+–$(CH_3)_2CO$), 141 (63, M^+–$HOCH_2CH_2NHCO$), 88 (100%); HRMS (ES$^+$) $C_{11}H_{20}NO_4$ [MH^+] requires 230.1387; found 230.1389.

***syn*-3-(2-Hydroxyethyl)-5-methyl-6-phenyl-1,3-oxazinane-2,4-dione 16**[27]. Reaction of *syn*-3-(3-hydroxy-2-methyl-3-phenylpropanoyl)-1,3-oxazolidin-2-one **3b** (0.150 g, 0.60 mmol) with a 1.0 M solution of Et_2Zn in toluene (0.06 mL, 0.06 mmol) in CH_2Cl_2 (3 mL), according to general procedure D, afforded the title compound *syn*-**16** (0.147 g, 0.58 mmol) in 97% yield and 95% de as a colourless oil, ν_{max}(neat)/cm^{-1} 3447 (br, OH), 1755 (C=O)$_{ox}$, 1703 (C=O); δ_H(300 MHz, $CDCl_3$) 1.01 (3H, d, *J* 7.5, C*H*$_3$), 2.17 (1H, s, O*H*), 2.99 (1H, qd, *J* 7.5, 3.5, C*H*CH$_3$), 3.75–3.82 (2H, m, C*H*$_2$OH), 3.97 (1H, app dt, *J* 14.0, 5.5, C*H*$_A$H$_B$N), 4.05 (1H, app dt, *J* 14.0, 5.5, CH$_A$*H*$_B$N), 5.62 (1H, d, *J* 3.5, C*H*Ph), 7.24–7.38 (5H, m, Ar–*H*); δ_C($CDCl_3$) 10.4, 41.5, 44.6, 61.2, 78.1, 126.0, 129.2, 129.4, 134.4, 152.4, 173.2; *m/z* (CI$^+$, NH_3) 267 (15, MNH_4^+), 206 (47, MH^+–CO_2), 105 (100%); HRMS (ES$^+$) $C_{13}H_{16}NO_4$ [MH^+] requires 250.1079, found 250.1081. Reaction of *syn*-1,3-oxazinane-2,4-dione **16** (0.100 g, 0.40 mmol) with a 0.5 M solution of KHMDS in toluene (0.91 mL, 0.6 mmol) in THF (3 mL), according to general procedure C, gave (*E*)-**4b** (0.068 g, 0.33 mmol) in 82% yield and in 95% de.

***syn*-3-(2-Hydroxyethyl)-5-isopropyl-6-[(*E*)-1-propenyl]-1,3-oxazinane-2,4-dione 17.** Reaction of *syn*-3-[(*E*)-3-hydroxy-2-isopropyl-4-hexenoyl]-1,3-oxazolidin-2-one **3i** (0.200 g, 0.83 mmol) with a 1.0 M solution of Et_2Zn in toluene (0.08 mL, 0.08 mmol) in CH_2Cl_2 (5 mL), according to general procedure D, afforded the title compound *syn*-**17** (0.129 g, 0.54 mmol) in 65% yield and >95% de as a colourless oil, ν_{max}(neat)/cm^{-1} 3430 (br, OH), 1755 (C=O)$_{ox}$, 1699 (C=O); δ_H(300 MHz, $CDCl_3$) 0.97 (3H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 1.03 (3H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 1.71 (3H, d, *J* 7.0, C*H*$_3$CH=CH), 1.97 (1H, t, *J* 5.5, O*H*), 2.10 (1H, m, *J* 7.0, 4.5, C*H*(CH$_3$)$_2$), 2.55 (1H, dd, *J* 7.0, 4.5, C*H*^{i}Pr), 3.74 (2H, app dt, *J* 5.5, 5.5, C*H*$_2$OH), 3.94–3.98 (2H, m, C*H*$_2$N), 4.92 (1H, app t, *J* 7.0, C*H*CH=CHCH$_3$), 5.47 (1H, dd, *J* 15.0, 7.0, CH$_3$CH=C*H*), 5.91 (1H, dq, *J* 15.0, 7.0, CH$_3$C*H*=CH); δ_C($CDCl_3$) 17.0, 19.7, 20.3, 24.8, 43.2, 49.5, 60.1, 76.6, 122.1, 132.7, 151.3, 169.7; *m/z* (EI$^{+\bullet}$) 241 (41, $M^{+\bullet}$), 198 (100%, $M^{+\bullet}$–$CO_2^{\bullet}$); HRMS (ES$^+$) $C_{12}H_{19}NO_4$ [MH^+] requires 241.1314, found 241.1313. Reaction of *syn*-1,3-oxazinane-2,4-dione **17** (0.010 g, 0.04 mmol) with a 0.5 M solution of KHMDS in toluene (0.09 mL, 0.06 mmol) in THF (3 mL), according to general procedure C, gave (2*E*,4*E*)-**4i** (0.007 g, 0.035 mmol) in 88% yield and in 60% de.

***anti*-3-(3-Hydroxy-2-methyl-3-phenylpropanoyl)-1,3-oxazolidin-2-one 18**[27]. Magnesium chloride (0.033 g, 0.35 mmol), triethylamine (0.97 mL, 6.99 mmol), benzaldehyde (0.43 mL, 4.19 mmol) and trimethylsilyl chloride (0.67 mL, 5.24 mmol) were added to a solution of 3-propionyl-1,3-oxazolidin-2-one **2a** (0.500 g, 3.50 mmol) in ethyl acetate (7 mL). The reaction mixture was stirred for 24 hours, and then filtered through a plug of silica which was then washed with Et_2O (10 ml). The organic layer was concentrated *in vacuo*, before addition of methanol (2 drops) and trifluoroacetic acid. The solvent was then removed before purification through silica gel chromatography (30% ethyl acetate–petrol) to afford the title compound *anti*-**18** (0.290 g, 1.16 mmol) in 33% yield as a white crystalline solid, mp 102–104 °C (lit,[27] 107–107.5 °C); ν_{max}(KBr disc)/cm^{-1} 3446 (s, OH), 1783 (C=O)$_{ox}$, 1665 (C=O); δ_H(300 MHz, $CDCl_3$) 1.05 (3H, d, *J* 7.0, C*H*$_3$), 2.87 (1H, d, *J* 5.0, O*H*), 4.00–4.06 (2H, m, C*H*$_2$N), 4.28 (1H, dq, *J* 8.5, 7.0, C*H*CH$_3$), 4.36–4.45 (2H, m, C*H*$_2$O), 4.78 (1H, dd, *J* 8.5, 5.0, C*H*OH), 7.26–7.43 (5H, m, Ar–*H*); δ_C($CDCl_3$) 15.2, 43.1, 44.8, 62.4, 77.5, 127.1, 128.5, 129.0, 142.1, 153.9, 176.9; *m/z* (CI$^+$, NH_3) 267 (94, MNH_4^+), 250 (48, MH^+), 105.1 (100%); HRMS (ES$^+$) $C_{13}H_{16}NO_4$ [MH^+] requires 250.1079, found 250.1079. Reaction of *anti*-aldol **18** (0.100 g, 0.4 mmol) with a 0.5 M solution of KHMDS in toluene (1.20 mL, 0.6 mmol) in THF (3 mL), according to general procedure C, gave (*E*)-**4b** (0.061 g, 0.3 mmol) in 74% yield and in 95% de.

***anti*-3-(2-Hydroxyethyl)-5-methyl-6-phenyl-1,3-oxazinane-2,4-dione 19**[27]. Reaction of *anti*-3-(3-hydroxy-2-methyl-3-phenylpropanoyl)-1,3-oxazolidin-2-one **18** (0.050 g, 0.20 mmol) with a 1.0 M solution of Et_2Zn in toluene (0.02 mL, 0.02 mmol) in CH_2Cl_2 (1 mL), according to general procedure D, afforded the title compound *anti*-**19** (0.047 g, 0.19 mmol) in 96% yield and >95% de as a white solid, ν_{max}(neat)/cm^{-1} 3435 (br, OH), 1755 (C=O)$_{ox}$, 1694 (C=O); δ_H(300 MHz, $CDCl_3$) 1.02 (3H, d, *J* 7.0, C*H*$_3$), 2.21 (1H, br s, O*H*), 2.89 (1H, qd, *J* 11.5, 7.0, C*H*(CH$_3$)), 3.77–3.80 (2H, app t, *J* 5.5, C*H*$_2$OH), 3.94 (1H, ddd, *J* 14.0, 6.0, 4.5, C*H*$_A$H$_B$N), 4.06 (1H, app dt, *J* 14.0, 5.5, CH$_A$*H*$_B$N), 5.04 (1H, d, *J* 11.5, C*H*Ph), 7.24–7.38 (5H, m, Ar–*H*); δ_C($CDCl_3$) 10.1, 40.4, 43.5, 59.6, 80.5, 126.1, 127.9, 128.7, 134.2, 151.1, 170.5; *m/z* (CI$^+$, NH_3) 267 (MNH_4^+, 100%), 250 (46, MH^+), 208 (55), 206 (87%, MH^+–CO_2); HRMS $C_{13}H_{16}NO_4$ (ES$^+$) [MH^+] requires 250.1079, found 250.1077. Reaction of *anti*-1,3-oxazinane-2,4-dione **19** (0.020 g, 0.075 mmol) with a 0.5 M solution of KHMDS in toluene (0.18 mL, 0.012 mmol) in THF (3 mL), according to general procedure C, gave (*E*)-**4b** (0.012 g, 0.006 mmol) in 80% yield and in 95% de.

(*E*)-3-Cyclohexyl-2-isopropyl-2-propenoic acid 26a[38]. Hydrolysis of (*E*)-3-cyclohexyl-*N*-(2-hydroxyethyl)-2-isopropyl-2-propenamide **4a** (0.053 g, 0.22 mmol) in 6.0 M HCl (2 mL), according to general procedure E, afforded the title compound (*E*)-**26a** (0.043 g, 0.22 mmol) in 99% yield and >95% de as a colourless oil, ν_{max}(neat)/cm^{-1} 3450 (br, OH), 1677 (C=O), 1621 (C=C)$_{conj}$; δ_H(300 MHz, $CDCl_3$) 0.90–1.30 (6H, m, Cy-*H*), 1.13 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 1.52–1.72 (4H, m, Cy-*H*), 2.33 (1H, dtt, *J* 10.5, 10.0, 3.5, C*H*), 2.84 (1H, septet, *J* 7.0, C*H*(CH$_3$)$_2$), 6.54 (1H, d, *J* 10.0, C*H*=CCH$_3$), 10.26 (1H, br s, COO*H*); δ_C($CDCl_3$) 20.2, 24.5, 26.4, 31.3, 31.9, 36.4, 134.1, 148.2, 172.7.; *m/z* (EI$^{+\bullet}$) 197.3 (15%, $MH^{+\bullet}$), 196.3 (15%, $M^{+\bullet}$); HRMS (ES$^+$) $C_{12}H_{20}O_2$ [MH^+] requires 196.1458; found 196.1454.

(*E*)-2-Methyl-3-phenyl-2-propenoic acid 26b. Hydrolysis of (*E*)-*N*-(2-hydroxyethyl)-2-methyl-3-phenyl-2-propenamide **4b** (0.048 g, 0.23 mmol) in 6.0 M HCl (3 mL), according to general procedure E, afforded the title compound (*E*)-**26b** (0.036 g, 0.22 mmol) in 95% yield and >95% de as a colourless oil, ν_{max}(neat)/cm^{-1} 3445 (br, OH), 1668 (C=O), 1616 (C=C)$_{conj}$; δ_H(300 MHz, $CDCl_3$) 2.08 (s, 3H, CH=CC*H*$_3$), 7.26–7.36 (5H, m, Ar–*H*), 7.77 (1H, s, C*H*=CCH$_3$), 11.36 (1H, br s, COO*H*); δ_C($CDCl_3$) 12.7, 126.5, 127.4, 127.7, 128.8, 134.5, 140.1, 173.4; *m/z* (EI$^+$) 162.1 (68%, $M^{+\bullet}$), 161.0 (36%, $M^{+\bullet}$–H$^{\bullet}$), 117.2 (58%, $M^{+\bullet}$–COOH$^{\bullet}$); HRMS (ES$^+$) $C_{10}H_{10}O_2$ [MH^+] requires 162.0675; found 162.0672.

(*E*)-2-Methylpenten-2-oic acid 26c. Hydrolysis of (*E*)-*N*-(2-hydroxyethyl)-2-methyl-2-pentenamide **4c** (0.300 g, 1.91 mmol) in 6.0 M HCl (5 mL), according to general procedure E, afforded the title compound (*E*)-**26c** (0.230 g, 2.02 mmol) in 91% yield and >95% de as a low-melting white solid, ν_{max}(neat)/cm^{-1} 3429 (br, OH), 1700 (C=O), 1646 (C=C); δ_H(300 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.5, CH$_2$C*H*$_3$), 1.76 (3H, d, *J* 1.0, CH=CC*H*$_3$), 2.14 (2H, app pentet, *J* 7.5, C*H*$_2$CH$_3$), 6.83 (1H, tq, 7.5, 1.0, C*H*=CCH$_3$), 11.70 (1H, br s, COO*H*); δ_C($CDCl_3$) 12.2, 13.2, 22.6, 126.8, 147.2, 174.3.

(*E*)-2-Benzyl-2-decenoic acid 26d. Hydrolysis of (*E*)-2-benzyl-*N*-(2-hydroxyethyl)-2-decenamide **4d** (0.200 g, 0.58 mmol) in 6.0 M HCl (5 mL), according to general procedure E, afforded the title compound (*E*)-**26d** (0.143 mg, 0.55 mmol) in 95% yield and >95% de, δ_H(300 MHz, $CDCl_3$) 0.80 (3H, t, *J* 7.0, C*H*$_3$), 1.12–1.25 (8H, m, Alk-*H*), 1.29–1.38 (2H, m, C*H*$_2$CH$_2$CH=C), 2.19 (2H, app q, *J* 7.5, C*H*$_2$CH=C), 3.58 (2H, s, C*H*$_2$Ph), 6.70 (1H, s, C*H*=CBn); 6.97–7.17 (5H, m, Ar–*H*); 10.70 (1H, br s, COO*H*); δ_C($CDCl_3$) 13.0, 21.6, 27.5, 28.0, 28.2, 28.3, 30.7, 31.2, 125.0, 127.2, 127.3, 129.2, 138.5, 146.1, 171.9; *m/z* (EI$^{+\bullet}$) 260.3 (66, $M^{+\bullet}$), 242 (9, $M^{+\bullet}$–H_2O), 161 (14, $M^{+\bullet}$–CH$_3$(CH$_2$)$_6^{\bullet}$), 91 (100%); HRMS (ES$^+$) $C_{17}H_{28}NO_2$ [MNH_4^+] requires 278.2120; found 278.2118.

(2*E*,4*E*)-2-Methyl-5-phenyl-2,4-pentadienoic acid 27[39]. Hydrolysis of (*E*,*E*)-*N*-(2-hydroxyethyl)-2-methyl-5-phenyl-2,4-pentadienamide **4j** (0.200g, 0.85 mmol) in 6.0 M HCl (5 mL), according to general procedure E, afforded the title compound (*E*,*E*)-**27** (0.158 g, 0.45 mmol) in 77% yield and >95% de as a pale brown solid, mp 158–160 °C (lit,[39] 160.0–162.5 °C); ν_{max}(KBr disc)/cm^{-1} 3445 (br, OH), 1683 (C=O), 1622 (C=C)$_{conj}$; δ_H(300 MHz, $CDCl_3$) 1.98 (3H, d, *J* 1.1, CH_3), 6.83 (1H, d, *J* 15.5, CHCH=C*H*Ph), 7.00 (1H, dd, *J* 15.5, 11.5, CH–C*H*=CHPh), 7.17–7.45 (6H, m, C*H*–CH=CHPh, Ar–H), 11.00 (1H, br s, COO*H*); δ_C($CDCl_3$) 11.5, 122.7, 125.4, 126.2, 127.8, 127.9, 135.4, 139.2, 139.6, 173.0; *m*/*z* (EI$^{+\bullet}$) 188 (33, M$^{+\bullet}$), 143 (62, M$^{+\bullet}$–COOH$^{\bullet}$), 128 (80, M$^{+\bullet}$–COOH–CH_3), 115 (100%, M$^{+\bullet}$–C(CH_3)COOH–H$^+$); HRMS (ES$^+$) $C_{12}H_{16}NO_2$ [MNH_4^+] requires 206.1176; found 206.1175.

2-[(*E*)-1-Methyl-2-phenyl-1-ethenyl]-4,5-dihydro-1,3-oxazole 28. Reaction of (*E*)-*N*-(2-hydroxyethyl)-2-methyl-3-phenyl-2-propenamide **4b** (0.570 g, 2.78 mmol) with thionyl chloride (0.89 mL, 12.20 mmol) in CH_2Cl_2 (15 mL), according to general procedure F, gave the title compound (*E*)-**28** (0.503 g, 2.69 mmol) in 97% yield and >95% de as a pale yellow oil, ν_{max}(neat)/cm^{-1} 1707 (C=N), 1640 (C=C); δ_H(300 MHz, $CDCl_3$) 2.21 (3H, d, *J* 1.5, CH=CCH_3), 4.01 (2H, app t, *J* 9.5, CH_2N), 4.36 (2H, app t, *J* 9.5, CH_2O), 7.12 (1H, d, *J* 1.5, CH=C(Me)), 7.35–7.40 (5H, m, Ar–*H*); δ_C($CDCl_3$) 15.4, 55.4, 67.9, 125.7, 128.2, 128.7, 129.9, 135.6, 136.7, 167.3; *m*/*z* (EI$^{+\bullet}$) 187 (27, M$^{+\bullet}$), 186 (100, M$^{+\bullet}$–H$^{\bullet}$), 129 (7, M$^{+\bullet}$–OCH_2CH_2N), 115 (25%, CH_3CCPh^+); HRMS (ES$^+$) $C_{12}H_{13}NO$ [MH^+] requires 187.0997; found 187.0998.

2-[(*E*)-1-Methyl-1-butenyl]-4,5-dihydro-1,3-oxazole 29. Reaction of (*E*)-*N*-(2-hydroxyethyl)-2-methyl-2-pentenamide **4c** (0.112 g, 0.71 mmol) with thionyl chloride (0.26 mL, 3.57 mmol) in CH_2Cl_2 (4 mL), according to general procedure F, gave the title compound (*E*)-**29** (0.087 g, 0.63 mmol) in 88% yield and >95% de as a colourless oil, ν_{max}(neat)/cm^{-1} 1700 (C=N), 1653 (C=C); δ_H(300 MHz, $CDCl_3$) 0.97 (3H, t, *J* 7.6, CH_2CH_3), 1.85 (3H, s, CH=CCH_3), 2.12 (2H, app pentet, *J* 7.5, CH_2CH$_3$), 3.86 (2H, t, *J* 9.5, CH_2N), 4.20 (2H, t, *J* 9.5, CH_2O), 6.34 (1H, t, *J* 7.4, C*H*=CCH$_3$); δ_C($CDCl_3$) 13.5, 13.7, 22.1, 55.1, 67.5, 123.9, 140.1, 166.8; *m*/*z* (EI$^{+\bullet}$) 139 (55%, M$^{+\bullet}$), 124 (100%, M$^{+\bullet}$–$CH_3^{\bullet}$); HRMS (ES$^+$) $C_8H_{14}NO$ [MH^+] requires 140.1070; found 140.1072.

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which corresponds to the structure of aldol **3i** reported in this paper. Furthermore, we were unable to reproduce the >95% de reported for the elimination reaction of *syn*-aldol **3i** to afford (*E*)-amide **4i**, and have concluded that this value is also incorrect, and must have arisen from unintentional fractional crystallisation of the crude reaction product prior to ^{1}H NMR spectroscopic analysis.

30 The ratio of aldol diastereomers **8a/9a** and **8c/9c** produced in these reactions was inferred from observation of the relative heights of the resonances of each diastereoisomer in the ^{13}C NMR spectra of each crude reaction product.

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Stereoselective Rearrangement of β-Hydroxy-*N*-acyloxazolidin-2-ones to Afford *N*-2-Hydroxyethyl-1,3-oxazinane-2,4-diones

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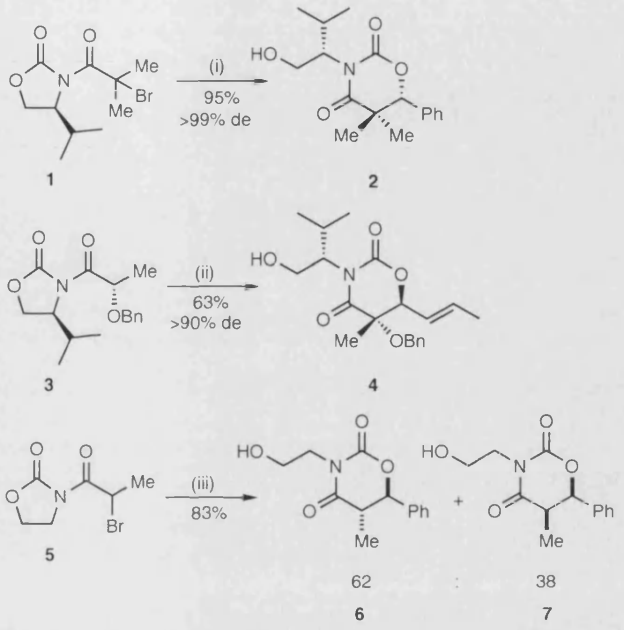
Abstract: Zinc alkoxides of *syn*- or *anti*-β-hydroxy-*N*-acyloxazolidin-2-ones undergo stereoselective rearrangement to afford their corresponding *syn*- or *anti*-*N*-2-hydroxyethyl-1,3-oxazinane-2,4-diones in good yield.

Key words: aldol reaction, diastereoselective, intramolecular rearrangement, 1,3-oxazinane-2,4-dione, zinc alkoxide

Benzo-1,3-oxazinane-2,4-diones have often been screened for activity as potential drug candidates,[1] and a range of synthetic methods is available for their preparation.[2] Synthetic routes towards other types of 1,3-oxazinane-2,4-dione are less well established, however,[3] and as a consequence their biological activity is less well explored. We were interested in preparing new types of 1,3-oxazinane-2,4-dione as potential synthetic intermediates,[4] or as novel medicinal agents,[5] and now report that zinc alkoxides of β-hydroxy-*N*-acyloxazolidin-2-ones undergo stereoselective rearrangement to afford their corresponding *N*-2-hydroxyethyl-5,6-disubstituted-1,3-oxazinane-2,4-diones in good yield.

Oxazolidin-2-ones have proven particularly useful as chiral auxiliaries in asymmetric aldol reactions for the preparation of chiral β-hydroxy acid derivatives.[6] For example, boron,[7] titanium,[8] and germanium enolates[9] of chiral *N*-acyloxazolidin-2-ones react with aldehydes to afford 'Evans' or 'non-Evans' *syn*-aldol products in high de. Alternatively, boron enolates of chiral *N*-acyloxazolidin-2-ones in the presence of excess Et_2AlCl,[10] their chromium enolates,[11] or Evans' recently published magnesium halide-catalysed protocol,[12] all result in *anti*-aldol products in high de. Whilst these procedures normally afford their respective aldol products in good yield and high de, a number of reports has described the formation of *N*-2-hydroxyethyl-1,3-oxazinane-2,4-diones as unexpected rearrangement products.[13,14] For example, reaction of a tin enolate derived from *N*-acyloxazolidin-2-one **1** with benzaldehyde resulted in formation of 1,3-oxazinane-2,4-dione **2** in >99% de,[15] whilst reaction of the lithium enolate of **3** with crotonaldehyde in the presence of $Ti(Oi\text{-}Pr)_3Cl$ gave 1,3-oxazinane-2,4-dione **4** in >90% de.[4] Alternatively, Terashima et al. reported that reaction of a zinc enolate derived from **5** with benzaldehyde at 0 °C afforded a 62:38 mixture of (*rac*)-*anti*-1,3-oxazinane-2,4-dione **6** and (*rac*)-*syn*-1,3-oxazinane-2,4-dione **7** in 83% yield (Scheme 1).[16]



Scheme 1 *Reagents and conditions*: (i) $SnCl_2$, $LiAlH_4$, THF, PhCHO, 20 °C; (ii) LDA, THF, –78 °C, $Ti(Oi\text{-}Pr)_3Cl$ (3.3 equiv), *trans*-crotonaldehyde; (iii) Zn, THF, PhCHO, 0 °C.

Whilst no *N*-acyloxazolidin-2-one aldol intermediates were isolated in these rearrangement reactions, these reports clearly implied that tin-, titanium- or zinc alkoxides of β-hydroxy-*N*-acyloxazolidin-2-ones could rearrange to their corresponding 1,3-oxazinane-2,4-diones in high de. We therefore decided to investigate whether suitable conditions could be identified which would enable the stereoselective rearrangement of diastereoisomerically pure β-hydroxy-*N*-acyloxazolidin-2-ones to occur, thus affording the corresponding 1,3-oxazinane-2,4-diones in good yield and in high de.

Therefore, a series of twelve racemic and enantiomerically pure *N*-acyloxazolidin-2-one-*syn*-aldols **9a–l** was prepared in high de via reaction of the boron enolates of *N*-acyloxazolidin-2-ones **8a–d** with a series of commercially available aldehydes,[17] according to well established literature precedent.[18] Given the precedent of Terashima et al.,[16] we proposed that conversion of *syn*-aldols **9a–l** into their corresponding zinc alkoxides would result in clean

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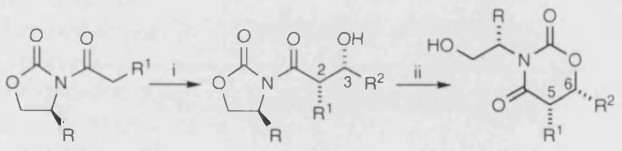
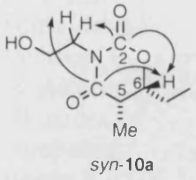
rearrangement to afford their corresponding *syn*-1,3-oxazinane-2,4-diones **10a–l** in high de.[19] Consequently, it was found that treatment of *syn*-aldol **9a** with a commercially available solution of 10 mol% Et_2Zn in CH_2Cl_2 at room temperature resulted in a clean rearrangement reaction to afford its corresponding *syn*-1,3-oxazinane-2,4-dione **10a** in >95% de, and 58% isolated yield.[20] The structure of *syn*-1,3-oxazinane-2,4-dione **10a** was confirmed by carrying out a HMBC ^1H-^{13}C NMR correlation experiment which clearly revealed cross-peaks between the ^{13}C resonance of its C-2 carbonyl, and the ^1H resonances of its *H*-6, and *N*-CH_2 protons (Figure 1). Zinc alkoxides of seven further racemic and enantiomerically pure *syn*-aldols **9b–h** were then generated under identical conditions, affording their corresponding *syn*-1,3-oxazinane-2,4-diones **10b–h** in >95% de and in 65–94% isolated yield after chromatographic purification (Scheme 2, Table 1).[21] The structure of each *syn*-1,3-oxazinane-2,4-dione product was apparent from its ^1H NMR spectrum [$J_{(5,6)}$ = 3.0–4.5 Hz],[22] which also revealed a large upfield shift for their C-5 ring protons (<3.0 ppm), when compared to the corresponding resonances of the C-2 protons (>3.5 ppm) of their parent *syn*-aldols **9b–h**, respectively.

Whilst zinc alkoxides of *syn*-aldols **9a–h** rearranged cleanly to afford their corresponding *syn*-1,3-oxazinane-2,4-diones **10a–h** in >95% de, it was found that rearrangement of β-aryl-*syn*-aldols **9i–l** occurred with poorer stereocontrol, affording their corresponding *syn*-1,3-oxazinane-2,4-diones **10i–l** in only 70–90% de.



8a R = H, R^1 = Me,
8b R = H, R^1 = *i*Pr,
8c R = Bn, R^1 = Me,
8d R = Bn, R^1 = *i*Pr

Scheme 2 *Reagents and conditions*: (i) 9-BBN-OTf, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to –78 °C, R_2CHO, CH_2Cl_2; (ii) 10 mol% Et_2Zn, THF, toluene, r.t.



syn-**10a**

Figure 1 Selected resonances from a HMBC ^1H-^{13}C NMR correlation experiment on *syn*-**10a**.

In order to explain this partial loss in stereocontrol,[23] it was proposed that rearrangement of the zinc alkoxide of β-aryl-*syn*-aldol **11** to afford *syn*-1,3-oxazinane-2,4-dione alkoxide **12** was occurring in the presence of a competing reversible *retro*-aldol/aldol reaction pathway (Figure 2).[24] This pathway would enable partial equilibration of the

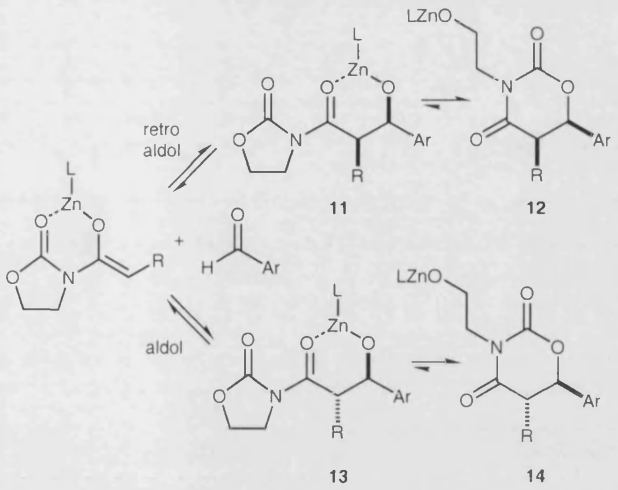


Figure 2 Reversible *retro*-aldol/aldol pathway to explain the formation of *anti*-1,3-oxazinane-2,4-diones **14**.

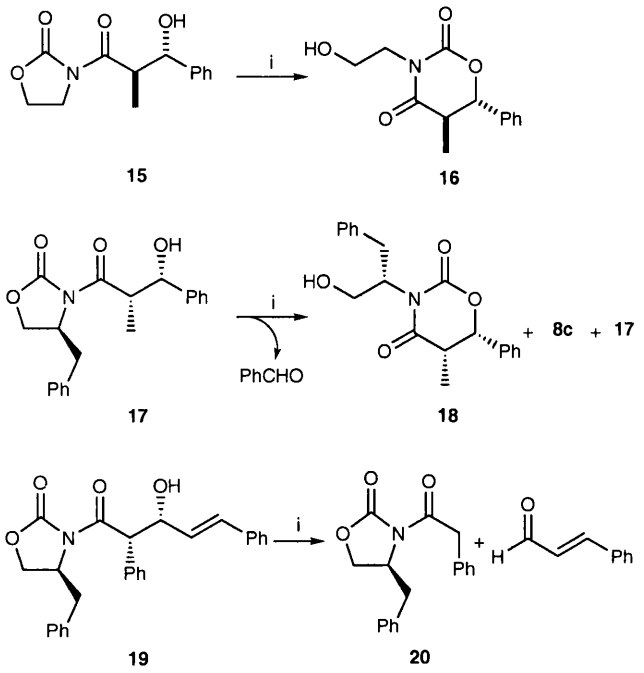
zinc alkoxide **11** to afford the zinc alkoxide of its respective β-aryl-*anti*-aldol **13**, which would then rearrange to afford the zinc alkoxide of its corresponding *anti*-1,3-oxazinane-2,4-dione **14**.

Further insight into the mechanism of this rearrangement reaction was gained on investigation of the reactivity of the zinc alkoxides of *anti*-β-aryl-aldol **15**, and the enantiomerically pure *syn*-aldols **17** and **19** (Scheme 3). Firstly, treatment of *anti*-β-aryl-aldol **15**[25] with 10 mol% Et_2Zn resulted in clean rearrangement to afford *anti*-1,3-oxazinane-2,4-dione **16** [$J_{(5,6)}$ = 11.5 Hz][22] as a single product in >95% de.[26] This clearly demonstrated that the zinc alkoxide of *anti*-aldol **15** had rearranged to its respective

Table 1 Yields for Rearrangement of *N*-Acyl-oxazolidin-2-one-*syn*-aldols **9a–l** to Afford *syn*-1,3-Oxazinane-2,4-diones **10a–l**

Entry	1,3-Oxazinane-2,4-dione	R	R^1	R^2	de (%)	Yield (%)[a]
1	**10a**	H	Me	Et	>95	58
2	**10b**	H	*i*-Pr	Et	>95	88
3	**10c**	H	*i*-Pr	Cyclohexyl	>95	90
4	**10d**	H	*i*-Pr	(*E*)-MeCH=CH–	>95	65
5	**10e**	Bn	Me	Et	>95	94
6	**10f**	Bn	Me	*i*-Pr	>95	92
7	**10g**	Bn	Me	Cyclohexyl	>95	94
8	**10h**	Bn	*i*-Pr	Et	>95	90
9	**10i**	H	Me	Ph	90	82
10	**10j**	H	*i*-Pr	Ph	80	52
11	**10k**	H	*i*-Pr	*p*-$MeOC_6H_4$	80	61
12	**10l**	H	*i*-Pr	*p*-$O_2NC_6H_4$	70	51

[a] Yields are for pure *syn*-1,3-oxazinane-2,4-diones **10a–l** isolated after chromatographic purification.



Scheme 3 *Reagents and conditions*: (i) 10 mol% Et_2Zn, THF, toluene, r.t.

anti-1,3-oxazinane-2,4-dione **16** with no loss of stereocontrol. Secondly, treatment of β-aryl-*syn*-aldol **17** under the same conditions resulted in a mixture of *syn*-1,3-oxazinane-2,4-dione **18** [>90% de, $J_{(5,6)}$ = 3.5 Hz], *N*-propionyloxazolidin-2-one **8c**, and recovered starting material **17**. Therefore, it is proposed that formation of **8c** and benzaldehyde in this reaction arises from *syn*-aldol **17** undergoing a *retro*-aldol reaction. The existence of this *retro*-aldol pathway was confirmed via treatment of α-aryl-β-styryl-*syn*-aldol **19** with Et_2Zn, which resulted in formation of *N*-phenylacetyloxazolidin-2-one **20**, and cinnamaldehyde as the only products. Therefore, it appears that the added electronic stabilisation afforded by the α-aryl-fragment of the zinc enolate of **20**, coupled with the conjugative stabilisation of cinnamaldehyde, is sufficient to ensure that *retro*-aldol fragmentation dominates the reactivity of the zinc alkoxide of *syn*-aldol **19**. We believe that these results, in conjunction with the observation that reaction of the zinc alkoxide of **5** with benzaldehyde affords a mixture of *anti*-**6** and *syn*-**7** (Scheme 1),[16] provide good evidence that the partial loss of stereocontrol observed for the rearrangement of zinc alkoxides of *syn*-β-aryl-aldols is a consequence of the competing *retro*-aldol/aldol pathway described in Figure 2.

In conclusion, we have demonstrated that zinc alkoxides of readily prepared *syn*- or *anti*-β-hydroxy-*N*-acyloxazolidin-2-ones undergo stereoselective rearrangement to afford a highly practical route to their corresponding *syn*- or *anti*-1,3-oxazinane-2,4-diones in good de.

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(16) Ito, Y.; Terashima, S. *Tetrahedron* **1991**, *47*, 2821.
(17) **Representative Synthetic Protocol for *syn*-Aldol Reactions.**
A 0.5 M solution of 9-BBN·OTf in hexanes (1.2 equiv) was added to a stirred solution of *N*-acyloxazolidin-2-one (1 equiv) in CH_2Cl_2 at 0 °C and allowed to stir for 5 min. *N,N*-Diisopropylethylamine (1.4 equiv) was added, the reaction stirred for 25 min at 0 °C and cooled to –78 °C. An aldehyde (1.1 equiv) was then added, the reaction was stirred for 2 h and the reaction then allowed to warm to 0 °C for 30 min. Then, pH 7.0 phosphate buffer was added, followed by a 2:1 solution of MeOH–H_2O_2. The reaction was extracted with CH_2Cl_2 (3 ×) and the combined organic extracts washed with aq $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated in vacuo to afford the appropriate *syn*-aldol which was then purified by chromatography.
(18) These conditions have been employed previously for asymmetric *syn*-aldol reactions using imidazolidin-2-one derived glycine enolates, see: Caddick, S.; Parr, N. J.; Pritchard, M. C. *Tetrahedron Lett.* **2000**, *41*, 5963.
(19) We have reported previously on a single example of this rearrangement see: Feuillet, F. J. P.; Robinson, D. E. J. E.; Bull, S. D. *Chem. Commun.* **2003**, 2184.
(20) **Representative Synthetic Protocol for Rearrangement Reaction.**
A 1.0 M solution of Et_2Zn in toluene (0.1 equiv) was added dropwise to a stirred solution of the *syn*-aldol (1 equiv) in CH_2Cl_2 at r.t. The reaction was stirred for 2 h. Then, sat. aq NH_4Cl was added and the reaction extracted with CH_2Cl_2 (3 ×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford the desired *syn*-1,3-oxazinane-2,4-dione which was then purified by chromatography.
(21) All new compounds were fully characterised. Selected data for new compounds:
***syn*-6-Ethyl-3-(2-hydroxyethyl)-5-isopropyl-1,3-oxazinane-2,4-dione (10b)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 [3 H, d, *J* = 7.0 Hz, $CH(CH_3)_2$], 1.00 (3 H, t, *J* = 7.5 Hz, CH_2CH_3), 1.02 [3 H, d, *J* = 7.0 Hz, $CH(CH_3)_2$], 1.60 (1 H, dqd, *J* = 14.0, 7.5, 5.0 Hz, $CH_AH_BCH_3$), 1.80 (1 H, ddq, *J* = 14.0, 9.0, 7.5 Hz, $CH_AH_BCH_3$), 2.08–2.21 [1 H, m, *J* = 7.0, 5.0, $CH(CH_3)_2$], 2.25 (1 H, br s, O*H*), 2.52 (1 H, dd, *J* = 5.0, 4.0 Hz, C*Hi*-Pr), 3.74 (2 H, app t, *J* = 5.5 Hz, CH_2OH), 3.89 (1 H, app dt, *J* = 14.0, 5.5 Hz, CH_AH_BN), 4.01 (1 H, app dt, *J* = 14.0, 5.5 Hz, CH_AH_BN), 4.39 (1 H, ddd, *J* = 9.0, 5.0, 4.0 Hz, C*H*O). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.0, 18.8, 21.2, 22.3, 14.5, 43.1, 48.4, 59.8, 78.0, 151.6, 170.0. IR: 3436 (br, OH), 1749 (C=O), 1691 (C=O) cm^{-1}.
***syn*-3-(2-Hydroxyethyl)-5-isopropyl-6-[(*E*)-1-propenyl]-1,3-oxazinane-2,4-dione (10d)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 [3 H, d, *J* = 7.0, $CH(CH_3)_2$], 1.03 [3 H, d, *J* = 7.0 Hz, $CH(CH_3)_2$], 1.71 (3 H, d, *J* = 7.0 Hz, CH_3CH=CH), 1.97 (1 H, t, *J* = 5.5 Hz, O*H*), 2.10 [1 H, m, *J* = 7.0 Hz, $CH(CH_3)_2$], 2.55 (1 H, dd, *J* = 7.0, 4.5 Hz, C*Hi*-Pr), 3.74 (2 H, app dt, *J* = 5.5, 5.5 Hz, CH_2OH), 3.94–3.98 (2 H, m, CH_2N), 4.92 (1 H, app t, *J* = 7.0 Hz, C*H*O), 5.47 (1 H, ddd, *J* = 15.0, 7.0, 1.5 Hz, CH_3CH=C*H*), 5.91 (1 H, dq, *J* = 15.0, 7.0 Hz, CH_3CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.0, 19.7, 20.3, 24.8, 43.2, 49.5, 60.1, 76.6, 122.1, 132.7, 151.3, 169.7. IR: 3430 (br, OH), 1755 (C=O), 1699 (C=O) cm^{-1}.
(5*S*,6*R*)-3-[(*S*)-1-Benzyl-2-hydroxyethyl]-6-ethyl-5-methyl-1,3-oxazinane-2,4-dione (10e): $[\alpha]_D^{20}$ –6.4 (*c* 0.47, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (3 H, t, *J* = 7.5 Hz, CH_2CH_3), 0.99 (3 H, d, *J* = 7.5, CH_3CH), 1.33 (2 H, m, CH_2CH_3), 2.50 (1 H, qd, *J* = 7.5, 3.5 Hz, $CHCH_3$), 2.99 (1 H, dd, *J* = 14.0, 7.0 Hz, $PhCH_ACH_B$), 3.16 (1 H dd, *J* = 14.0, 10.5 Hz, $PhCH_ACH_B$), 3.68 (2 H, obscured m, C*H*O), 3.82 (1 H, dd, *J* = 12.0, 4.0 Hz, CH_AH_BOH), 4.01 (1 H, dd, *J* = 12.0, 7.0 Hz, CH_AH_BOH), 5.04 (1 H, app dtd, *J* = 10.5, 7.0, 4.0 Hz, CHN), 7.10–7.15 (5 H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.2, 9.5, 22.6, 33.7, 39.2, 56.5, 63.3, 78.4, 126.6, 128.5, 129.1, 137.4, 151.8, 173.1. IR: 3462 (br, OH), 1755 (C=O), 1700 (C=O) cm^{-1}.
(5*S*,6*R*)-3-[(*S*)-1-Benzyl-2-hydroxyethyl]-6-ethyl-5-isopropyl-1,3-oxazinane-2,4-dione (10h): $[\alpha]_D^{20}$ –6.8 (*c* 0.59, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (3 H, t, *J* = 7.5 Hz, CH_2CH_3), 0.85 [3 H, d, *J* = 7.0 Hz, $CH(CH_3)_2$], 0.92 [3 H, d, *J* = 7.0 Hz, $CH(CH_3)_2$], 1.31–1.46 (1 H, dqd, *J* = 14.0, 7.5, 5.0 Hz, $CH_AH_BCH_3$), 1.45–1.61 (1 H, m, $CH_AH_BCH_3$), 1.94–2.05 [1 H, m, $CH(CH_3)_2$], 2.18 (1 H, app t, *J* = 4.5 Hz, C*Hi*-Pr), 2.53 (1 H, br s, O*H*), 2.99 (1 H, dd, *J* = 14.0, 7.0 Hz, CH_AH_BPh), 3.13 (1 H, dd, *J* = 14.0, 10.5 Hz, CH_AH_BPh), 3.64 (1 H, obscured m, C*H*O), 3.82 (1 H, dd, *J* = 12.0, 4.0 Hz, CH_AH_BOH), 4.02 (1 H, dd, *J* = 12.0, 7.0 Hz, CH_AH_BOH), 5.04–5.14 (1 H, app dtd, *J* = 10.5, 7.0, 4.0 Hz, C*H*N), 7.08–7.22 (5 H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.4, 20.2, 22.6, 23.4, 25.5, 34.3, 50.2, 56.5, 63.7, 79.4, 127.0, 128.9, 129.5, 135.0, 152.5, 171.4. IR: 3423 (br, OH), 1754 (C=O), 1691 (C=O) cm^{-1}.
***syn*-3-(2-Hydroxyethyl)-5-methyl-6-phenyl-1,3-oxazinane-2,4-dione (10i)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (3 H, d, *J* = 7.5 Hz, CH_3), 2.17 (1 H, s, O*H*), 2.99 (1 H, qd, *J* = 7.5, 3.5 Hz, $CHCH_3$), 3.75–3.82 (2 H, m, CH_2OH), 3.97 (1 H, app dt, *J* = 14.0, 5.5 Hz, CH_AH_BN), 4.05 (1 H, app dt, *J* = 14.0, 5.5 Hz, CH_AH_BN), 5.62 (1 H, d, *J* = 3.5 Hz, C*H*O), 7.24–7.38 (5 H, m, Ph-*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.4, 41.5, 44.6, 61.2, 78.1, 126.0, 129.2, 129.4, 134.4, 152.4, 173.2. IR: 3447 (br, OH), 1755 (C=O), 1703 (C=O) cm^{-1}.
***syn*-3-(2-Hydroxyethyl)-5-isopropyl-6-(4-methoxyphenyl)-1,3-oxazinane-2,4-dione (10k)**: mp 79–81 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 [3 H, d, *J* = 7.0 Hz, $CH(CH_3)_2$], 0.98 (3 H, d, *J* = 7.0 Hz, $CH(CH_3)_2$], 1.96 [1 H, m, *J* = 7.0, 4.0 Hz, $CH(CH_3)_2$], 2.26 (1 H, br s, O*H*), 2.79 (1 H, t, *J* = 4.0 Hz, C*Hi*-Pr), 3.83 (3 H, s, $ArOCH_3$), 3.81–3.87 (2 H, m, CH_2OH), 4.02 (1 H, app dt, *J* = 14.0, 5.5 Hz, CH_AH_BN), 4.16 (1 H, app dt, *J* = 14.0, 5.5 Hz, CH_AH_BN), 5.71 (1 H, d, *J* = 4.0 Hz, C*H*O), 6.94 (2 H, d, *J* = 8.5 Hz, Ar-*H*), 7.29 (2 H, d, *J* = 8.5 Hz, Ar-*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, 23.1, 26.0, 44.7, 52.0, 55.7, 61.3, 78.4, 114.6, 126.7, 127.1, 152.9, 160.1, 171.4. IR: 3353 (br, OH), 1740 (C=O), 1691 (C=O) cm^{-1}.

(22) *syn*-1,3-Oxazinane-2,4-diones exhibit $J_{(5,6)}$ coupling constants of <4.5 Hz, whilst *anti*-1,3-oxazinane-2,4-diones exhibit $J_{(5,6)}$ coupling constants of >10.0 Hz; see ref. 13c, 14, 16.

(23) An alternative mechanism involving zinc alkoxide-catalysed epimerisation of the α-stereocentres of *syn*-β-aryl-aldols **9i–l** (or *syn*-β-aryl-1,3-oxazinane-2,4-diones **10i–l**) was discounted because their acidities are similar to those of the α-stereocentres of *syn*-β-alkyl-aldols **9a–k** that had been shown to rearrange with no loss of stereocontrol under these conditions.

(24) A similar reversible *retro*-aldol/aldol mechanism has been proposed to explain the diastereoselectivity observed for reaction of metal enolates of *N*-acyl-oxazolidin-2-ones with ketones, see:Bartroli, J.; Turmo, E.; Belloc, J.; Forn, J. *J. Org. Chem.* **1995**, *60*, 3000.

(25) *N*-Acyl-oxazolidin-2-one-*anti*-aldol **15** was prepared using Evans' magnesium halide-catalysed protocol, see ref. 12.

(26) ***anti*-3-(2-Hydroxyethyl)-5-methyl-6-phenyl-1,3-oxazinane-2,4-dione (16)**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (3 H, d, *J* = 7.0 Hz, CH_3), 2.21 (1 H, br s, O*H*), 2.89 (1 H, dq, *J* = 11.5, 7.0 Hz, $CHCH_3$), 3.77–3.80 (2 H, app t, *J* = 5.5 Hz, CH_2OH), 3.94 (1 H, dt, *J* = 14.0, 5.5 Hz, CH_AH_BN), 4.06 (1 H, app dt, *J* = 14.0, 5.5 Hz, CH_AH_BN), 5.04 (1 H, d, *J* = 11.5 Hz, C*H*Ph), 7.24–7.38 (5 H, m, Ph-*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.1, 40.4, 43.5, 59.6, 80.5, 126.1, 127.9, 128.7, 134.2, 151.1, 170.5. IR: 3435 (br, OH), 1755 (C=O), 1694 (C=O) cm^{-1}.

A novel strategy for the asymmetric synthesis of chiral cyclopropane carboxaldehydes†

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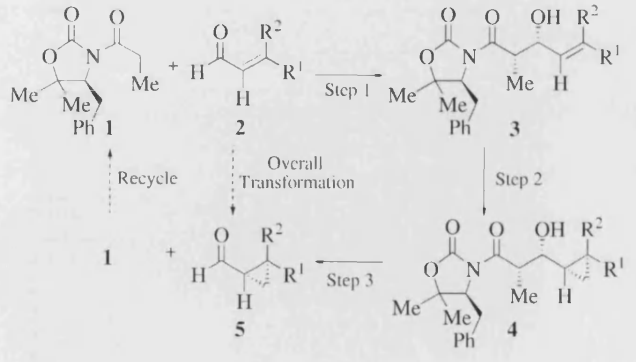
A new way of combining chiral auxiliaries and substrate-directable reactions for asymmetric synthesis is described that employs a three-step sequence of aldol–cyclopropanation–*retro*-aldol reactions for the stereoselective synthesis of enantiopure cyclopropane carboxaldehydes.

Chiral auxiliaries[1] and substrate-directable reactions[2] have often been combined to afford powerful synthetic protocols for the asymmetric synthesis of chiral building blocks for natural product synthesis.[3] In these approaches a chiral auxiliary is first employed to prepare a chiral intermediate containing a new stereogenic centre in high de. This new stereocentre is then employed to control the facial selectivity of a substrate-directable reaction to afford a second chiral intermediate containing further stereogenic centres. Finally, the second chiral intermediate is then cleaved to afford the chiral auxiliary and a chiral product.[4] We were interested in developing new ways of combining chiral auxiliaries and substrate-directable reactions for asymmetric synthesis, and now report herein on a novel three-step protocol that employs a sequence of aldol–cyclopropanation–*retro*-aldol reactions for the stereoselective synthesis of chiral cyclopropane carboxaldehydes in enantiopure form.[5]

The novel three-step protocol that was envisaged for the asymmetric synthesis of chiral cyclopropane carboxaldehydes is described in Scheme 1. Firstly, (*S*)-*N*-propionyl-5,5-dimethyl-oxazolidin-2-one **1**[6] would undergo a stereoselective aldol reaction with an α,β-unsaturated aldehyde substrate **2** to afford a *syn*-aldol product **3** in high de (Step 1). Secondly, stereoselective cyclopropanation of the allylic alcohol functionality of **3** would occur under the stereodirecting effect of its β-hydroxyl functionality to afford cyclopropane **4** in high de (Step 2). Finally, *retro*-aldol fragmentation of cyclopropane **4** would afford the desired chiral cyclopropane carboxaldehyde **5** and the chiral auxiliary fragment **1** that could then be recycled as required (Step 3).[7] The overall outcome of this three-step protocol would therefore be the stereoselective transformation of an achiral α,β-unsaturated aldehyde **2** into a chiral cyclopropane carboxaldehyde **5** in enantiopure form (Scheme 1).

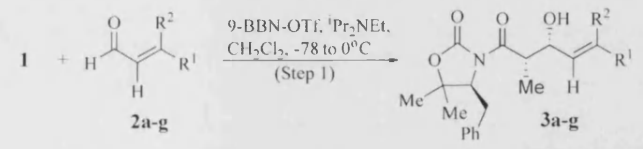


Scheme 1 Novel three-step strategy for the asymmetric synthesis of chiral cyclopropane carboxaldehydes.

The first step of this new strategy was well precedented since it had been reported previously that reaction of (*Z*)-boron enolates of *N*-acyl-oxazolidin-2-ones, with α,β-unsaturated aldehydes, gave *syn*-aldol products in high de.[8] Consequently, we found that treatment of (*S*)-*N*-propionyl-5,5-dimethyl-oxazolidin-2-one **1** with 9-BBN-OTf and $^{i}Pr_2NEt$ in CH_2Cl_2 at 0 °C, followed by cooling to −78 °C and addition of the appropriate α,β-unsaturated aldehyde **2a–g**,[9] gave a range of *syn*-aldol products **3a–g** in >95% de, and in acceptable 76–87% isolated yields (Table 1).[10] (*Z*)-*syn*-Aldol **3h** was prepared in >95% de and in an overall 60% yield, *via* an alternative two-step reaction sequence, involving reaction of the (*Z*)-boron enolate of **1** with oct-2-yn-al **6**,[11] followed by hydrogenation of the resultant *syn*-aldol product using Lindlar's catalyst (Scheme 2).[12]

We next determined conditions that would enable the alkene functionality of *syn*-aldol products **3a–h** to be cyclopropanated in high de.[13] It was found that treatment of *syn*-aldols **3a–h** with

Table 1 Asymmetric synthesis of *syn*-aldols **3a–g** in high de (Step 1)



2a-g **3a-g**

Entry	Aldehyde	R^1	R^2	Aldol	de (%)[a,b]	Yield (%)
1	**2a**	Ph-	H	**3a**	>95	80
2	**2b**	$Me(CH_2)_6$–	H	**3b**	>95	81
3	**2c**	*p*-$MeOC_6H_4$–	H	**3c**	>95	77
4	**2d**	*o*-$NO_2C_6H_4$–	H	**3d**	>95	87
5	**2e**	2-Furyl	H	**3e**	>95	85
6	**2f**	Me	Me	**3f**	>95	76
7	**2g**	Me	H	**3g**	>95	76

[a] The des of aldols **3a–g** were determined from ^1H NMR spectra of their crude reaction products. [b] Aldols **3a–g** exhibited $J_{(2',3')}$ coupling constants of between 2.0 and 6.0 Hz in their ^1H NMR spectra, consistent with the assigned *syn*-configuration.

† Electronic supplementary information (ESI) available: representative experimental details and data for the asymmetric synthesis of cyclopropane carboxaldehyde (*S,S*)-**5d**. See http://www.rsc.org/suppdata/cc/b5/b501847a/

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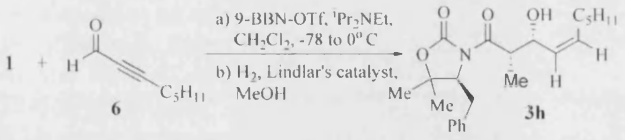
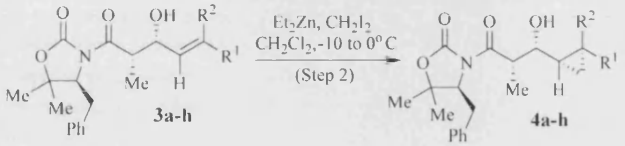


Scheme 2 Alternative two-step *syn*-aldol–hydrogenation protocol for the synthesis of *syn*-aldol **3h**.

Table 2 Cyclopropanation occurs under the stereocontrol of the β-hydroxy group to afford *syn*-cyclopropyl-aldols **4a–h** in high de (Step 2)



Entry	Aldol	R^1	R^2	Cyclopropane	de (%)[a]	Yield (%)
1	**3a**	Ph	H	**4a**	>95	95
2	**3b**	$Me(CH_2)_6$–	H	**4b**	>95	89
3	**3c**	*p*-$MeOC_6H_4$–	H	**4c**	>95	90
4	**3d**	*o*-$NO_2C_6H_4$–	H	**4d**	>95	90
5	**3e**	2-Furyl	H	**4e**	>95	92
6	**3f**	Me	Me	**4f**	>95	99
7	**3g**	Me	H	**4g**	>95	95
8	**3h**	H	C_5H_{11}–	**4h**	>95	96

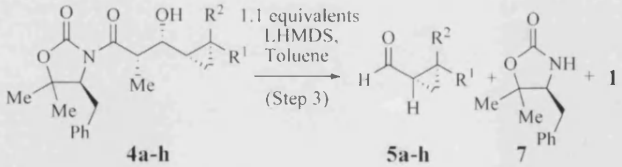
[a] The des of *syn*-cyclopropyl-aldols **4a–h** were determined from the ^{1}H NMR spectra of their crude reaction products.

Et_2Zn and CH_2I_2 in CH_2Cl_2 at a temperature between −10 and 0 °C resulted in a highly diastereoselective cyclopropanation reaction,[14] affording *syn*-cyclopropyl-aldols **4a–h** in >95% de and 89–99% yield (Table 2). Cyclopropanations of this type of allylic alcohol substrate under modified Furukawa conditions are normally *syn*-selective due to minimisation of $A^{1,3}$ strain in the transition state,[14] and as a consequence the configurations of *syn*-cyclopropyl-aldols **4a–h** were assigned accordingly.[15,16]

Conditions were next identified that would enable *syn*-cyclopropyl-aldols **4a–h** to undergo *retro*-aldol cleavage to afford their desired cyclopropane carboxaldehydes **5a–h**.[17] Extensive screening of a range of bases and conditions revealed that treatment of *syn*-cyclopropyl-aldols **4a–e** with LHMDS in toluene, at temperatures between 0 °C and 10 °C, resulted in clean *retro*-aldol cleavage to afford a mixture of the desired chiral cyclopropane carboxaldehydes **5a–e**, (*S*)-*N*-propionyl-5,5-dimethyl-oxazolidin-2-one **1**, and 5,5-dimethyl-oxazolidin-2-one **7** (<20%) with excellent mass recovery. Presumably, competing formation of **7** arises from partial decomposition of the lithium enolate of *N*-propionyl-oxazolidin-2-one **1** *via* a *retro*-ketene addition mechanism.[18] Purification of each *retro*-aldol reaction product by chromatography gave cyclopropane carboxaldehydes (*S,S*)-**5a–e** in >95% de and in 55–75% isolated yields (Table 3). The absolute configuration of cyclopropane carboxaldehydes (*S,S*)-**5a** and (*S,S*)-**5b** were confirmed from their positive specific rotations,[19,20] whilst the enantiomeric purity of (*S,S*)-**5b** was confirmed as >95% ee by conversion to its corresponding imidazolidinone using (*R,R*)-(+)-dimethyl-1,2-diphenyl-1,2-ethane-diamine as a chiral derivatising agent.[21]

Treatment of *syn*-cyclopropyl-aldols **4f** and **4g** with LHMDS at 0 °C also resulted in clean *retro*-aldol reactions, however attempted purification of aldehydes **5f** and **5g** by chromatography was less successful due to their inherent volatility which led to poor yields of aldehyde being isolated. Consequently, the *retro*-aldol reactions of cyclopropyl-aldols **4f** and **4g** were repeated using LHMDS in toluene-d_8 at 0 °C, and each reaction worked-up *via* addition of five drops of NH_4Cl_{aq}, before drying over $MgSO_4$. Resulting distillation of the respective crude reaction products afforded a solution of the desired aldehydes **5f** (>95% ee) and **5g** (>95% de) in toluene-d_8,[22] the yields of which were determined as 51% and 65% respectively *via* ^{1}H NMR spectroscopic analysis in the presence of a known concentration of 2,5-dimethylfuran as an

Table 3 Anionic *retro*-aldol reactions afford chiral cyclopropane carboxaldehydes **5a–h** in enantiopure form (Step 3)



Entry	Aldol	R^1	R^2	Aldehyde	Conditions	de (%)[a]	Yield (%)[c]
1	**4a**	Ph	H	**5a**	1 h / 0 °C	>95[24]	75
2	**4b**	$Me(CH_2)_6$–	H	**5b**	1 h / 0 °C	>95	73
3	**4c**	*p*-$MeOC_6H_4$–	H	**5c**	3 h / 5 °C	>95	63
4	**4d**	*o*-$NO_2C_6H_4$–	H	**5d**	5 h / 10 °C	>95	55
5	**4e**	2-Furyl	H	**5e**	1 h / 0 °C	>95	71
6	**4f**	Me	Me	**5f**	1 h / 0 °C	>95% ee[b]	51[d]
7	**4g**	Me	H	**5g**	1 h / 0 °C	>95	65[d]
8	**4h**	H	C_5H_{11}–	**5h**	1 h / 0 °C	>95[25]	61

[a] The des of cyclopropane carboxaldehydes **5a–h** were determined from the ^{1}H NMR spectra of their crude *retro*-aldol reaction products. [b] The ee of cyclopropane carboxaldehyde **5f** was determined *via* derivatisation with (*R,R*)-(+)-dimethyl-1,2-diphenyl-1,2-ethane-diamine.[21] [c] ^{1}H NMR spectroscopic analysis of the crude reaction products revealed that all cyclopropane carboxaldehydes had been formed in >70% yield. [d] Yields were determined from ^{1}H NMR spectroscopic analysis of the cyclopropane carboxaldehyde in toluene-d_8 in the presence of a known concentration of 2,5-dimethylfuran.[22]

internal standard (Table 3).[23] Finally, treatment of *cis*-cyclopropyl-aldol (*Z*)-**4h** with LHMDS at 0 °C also resulted in a clean *retro*-aldol reaction affording *cis*-cyclopropane carboxaldehyde (1*S*,2*R*)-**5h** in 61% yield,[24] with no epimerisation to its more stable (1*R*,2*R*)-epimer having occurred under the basic conditions used to facilitate the *retro*-aldol reaction.[25]

In summary, a novel three-step aldol–cyclopropanation–*retro*-aldol sequence for the direct asymmetric synthesis of enantiopure cyclopropane carboxaldehydes under non-oxidative/non-reductive conditions has been developed. This protocol demonstrates the potential of a novel synthetic strategy that employs a chiral auxiliary to *reversibly* generate a *temporary* stereocentre that is then employed as a stereodirecting group to control facial selectivity for a substrate-directable reaction. We anticipate that this new strategy will prove applicable to the combination of other types of chiral auxiliary and substrate-directable reaction, thus enabling its potential for asymmetric synthesis to be realised in a wide range of different reaction scenarios.

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An efficient synthesis of semiplenamide C

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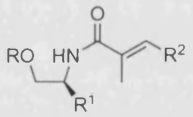
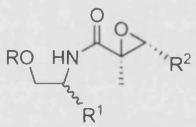
Abstract—Semiplenamides are anandamide-like fatty acid amide metabolites previously isolated from a marine cyanobacterium that display a range of biological activity. Novel *syn*-aldol/dehydration methodology has been developed for the stereoselective synthesis of the core (*E*)-α,β-unsaturated amide functionality of this class of natural product, and employed for the efficient synthesis of semiplenamide C.

Marine cyanobacteria produce a wide range of bioactive and structurally complex natural products, a number of which have been shown to be derived from modified fatty acid fragments.[1] Gerwick and co-workers have recently reported the isolation of a series of novel semiplenamide metabolites from the marine cyanobacterium *Lyngbya semiplena* that were shown to be structurally related to anandamide fatty acid amides.[2] All of the semiplenamides A–G **1a–g** (Fig. 1) displayed toxicity toward the brine shrimp model system, semiplenamides A, B, and G exhibited weak affinity for the rat cannabinoid CB1 receptor, whilst semiplenamide A was a moderate inhibitor of the anandamide membrane transporter.[2] Given this range of biological activity, we were interested in developing efficient methodology for their stereoselective syntheses, and now report herein on the development of novel aldol/dehydration methodology for the efficient synthesis of semiplenamide C **1c**.



1a Semiplenamide A; R = H, R^1 = H, R^2 = (3*E*)-*n*-$C_{17}H_{33}$-
1b Semiplenamide B; R = Ac, R^1 = H, R^2 = (3*E*)-*n*-$C_{17}H_{33}$-
1c Semiplenamide C; R = H, R^1 = Me, R^2 = *n*-$C_{13}H_{27}$-
1d Semiplenamide D; R = Ac, R^1 = Me, R^2 = *n*-$C_{17}H_{35}$-
1e Semiplenamide E; R = Ac, R^1 = Me, R^2 = *n*-$C_{15}H_{31}$-



1f Semiplenamide F; R = H, R^1 = (*S*)-Me, R_2 = *n*-$C_{15}H_{31}$-
1g Semiplenamide G, R = Ac, R^1 = Me, R_2 = *n*-$C_{15}H_{31}$-

Figure 1. Structures of semiplenamides A–G **1a–g**.

We have recently reported that potassium alkoxides of β-hydroxy-*N*-acyloxazolidinones **2** undergo stereoselective elimination to afford trisubstituted (*E*)-α,β-unsaturated amides **5**.[3] In these elimination reactions, the potassium alkoxide of **2** first undergoes intramolecular attack at its oxazolidin-2-one carbonyl, resulting in *O–O* carbonyl migration, to afford an intermediate 1,3-oxazinane-2,4-dione alkoxide **3**. Subsequent anion equilibration affords enolate **4** that then undergoes stereoselective elimination of carbon dioxide to afford the trisubstituted secondary amide (*E*)-**5** (Fig. 2).[4]

This novel elimination methodology appeared ideally suited to the synthesis of the core fatty acid amide fragments of the semiplenamides A–E **1a–e** that we proposed could be easily prepared according to the retro-synthetic strategy described in Figure 3. Therefore, reaction between the enolate of an L-alanine derived *N*-acyloxazolidin-2-one with an appropriate aldehyde would afford a *syn*-aldol product, whose potassium alkoxide would subsequently undergo elimination to afford the desired (*E*)-amide functionality.

Keywords: *N*-Acyl-oxazolidin-2-one; *syn*-Aldol; Elimination; Natural product.
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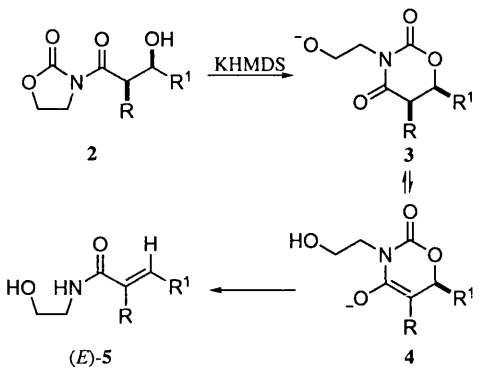


Figure 2. Intramolecular cyclization/elimination mechanism for formation of α,β-unsaturated amide (*E*)-**5**.

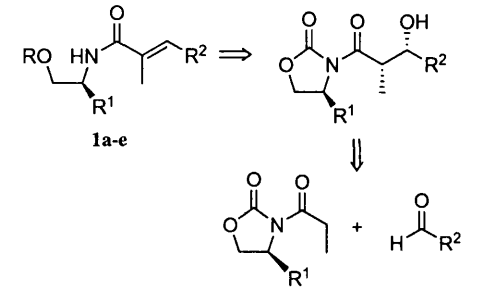
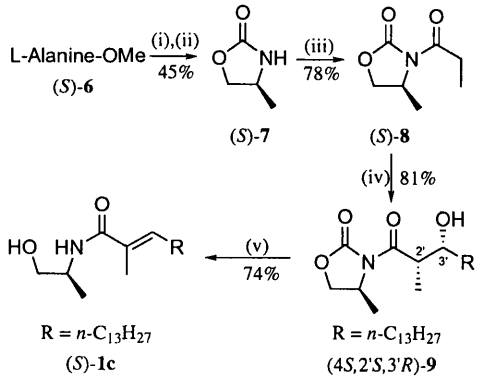


Figure 3. Retro-synthetic disconnection of semiplenamides A–E.



Scheme 1. Reagents and conditions: (i) $LiAlH_4$, Et_2O; (ii) $(EtO)_2CO$, KOEt, THF; (iii) *n*-BuLi, THF, −78 °C, EtCOCl; (iv) 9-BBN-OTf, $^iPr_2NEt$, CH_2Cl_2, 0 °C, n-$C_{13}H_{27}CHO$, −78 °C; (v) KO^{t}Bu, THF, −78 °C to rt.

Semiplenamide C **1c** was chosen as a representative synthetic target to develop this methodology, using L-alanine methyl ester (*S*)-**6** as an enantiopure starting material (Scheme 1). Reduction of (*S*)-**6** with $LiAlH_4$ in Et_2O, followed by treatment of the resultant (*S*)-amino-alcohol with diethyl carbonate under basic conditions, resulted in the formation of (*S*)-4-methyl-oxazolidin-2-one (*S*)-**7** in a 45% yield over two steps.[5] Subsequent treatment of (*S*)-**7** with *n*-BuLi in THF at −78 °C, followed by addition of propionyl chloride afforded *N*-propionyl-oxazolidin-2-one (*S*)-**8** in 78% yield.

Treatment of (*S*)-**8** with 1.1 equiv of 9-BBN-OTf and $^iPr_2NEt$ in CH_2Cl_2, followed by cooling to −78 °C, and addition of 1.1 equiv of tetradecanal,[6] resulted in *syn*-aldol **9** in >95% de, and in 81% yield after purification by chromatography.[7] The *syn*-stereochemistry of (4*S*,2′*S*,3′*R*)-aldol **9** was confirmed from the $J_{(2',3')}$ coupling constant of 3.0 Hz observed in its ^1H NMR spectrum.[8] The high levels of stereocontrol in this *syn*-aldol reaction are particularly noteworthy considering that facial selectivity is controlled by the sterically undemanding (4*S*)-methyl group of the oxazolidin-2-one fragment.

Generation of the potassium alkoxide of *syn*-aldol **9** via treatment with 1.1 equiv of KHMDS in toluene at 0 °C gave a low 23% yield of semiplenamide C (*S*)-**1c**, as well as *N*-propionyl-oxazolidin-2-one (*S*)-**8**, oxazolidin-2-one (*S*)-**7**, and tetradecanal as unwanted side-products arising from a competing retro-aldol cleavage pathway.[9] However, it was found that simply changing the base employed for deprotonation of *syn*-aldol **9** to KO^{t}Bu in THF at −78 °C resulted in a clean elimination reaction to afford semiplenamide C (*S*)-**1c** in 74% yield after purification by chromatography.[10]

In conclusion, we have developed efficient methodology for the synthesis of the core (*E*)-α,β-unsaturated amide fragments of semiplenamides A–E **1a–e**, and have applied this methodology to the first synthesis of semiplenamide C. Work is currently underway applying this approach to the stereoselective synthesis of the remaining semiplenamides, as well as for the synthesis of other natural and non-natural anandamide-like products.

Acknowledgements

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J = 7.0 Hz), 1.20–1.30 (24H, m), 1.35 (3H, d, J = 7.0 Hz), 2.40 (1H, br s, OH); 3.68 (1H, qd, J = 7.0 and 3.0 Hz, $H_{2'}$), 3.86 (1H, m, $H_{3'}$), 3.94 (1H, dd, J = 8.0 and 3.0 Hz, H_{5A}), 4.38 (1H, app t, J = 8.0 Hz, H_{5B}), 4.52 (1H, m, H_4).

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10. $[\alpha]_D$ for (*S*)-**1c** = −8.3 (*c* 0.6, $CHCl_3$); lit. $[\alpha]_D$ −5.0 (*c* 0.3, $CHCl_3$); all other spectroscopic data for (*S*)-**1c** were identical to that published in Ref. 2.

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An efficient asymmetric synthesis of grenadamide

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Abstract—The cyclopropane containing natural product grenadamide has been prepared in six steps using (*R*)-5,5-dimethyl-oxazolidin-2-one as a chiral auxiliary for asymmetric synthesis. Key synthetic steps include the use of the β-hydroxyl group of a *syn*-aldol product as a 'temporary' stereocentre to control the facial selectivity of a directed cyclopropanation reaction, as well as the use of phenylethylamine as a nucleophile for the direct aminolysis of an *N*-acyl-oxazolidin-2-one intermediate.

Grenadamide **1**, debromogrenadadiene **2** and grenadadiene **3** are natural products that were isolated from the marine cyanobacterium *Lyngbya majuscula*, by Sitachitta and Gerwick in 1998 (Fig. 1).[1] These structurally unique cyclopropyl fatty acid derived metabolites were shown to demonstrate cannabinoid receptor binding activity, as well as cytotoxicity towards cancer cells. Baird and co-workers subsequently confirmed the absolute configuration of the cyclopropane fragment of grenadamide **1** as (*R*,*R*) via total synthesis. Their synthesis required 14 steps, with an enzymatic desymmetrisation step being employed to introduce the stereogenic centres of the cyclopropane fragment.[2] We thought that this approach appeared a little complicated since this structurally simple natural product contains only two stereogenic centres. Consequently, we now report an alternative asymmetric synthesis of grenadamide **1** in six steps from the chiral auxiliary (*R*)-4-benzyl-5,5-dimethyl-oxazolidin-2-one **15**.

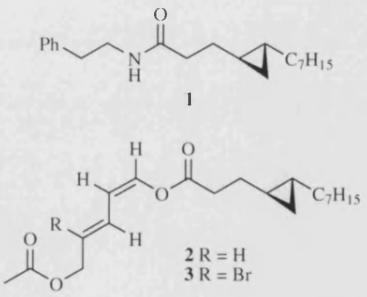

Figure 1. Structures of grenadamide **1**, debromogrenadadiene **2** and grenadadiene **3**.

We are interested in developing novel synthetic strategies that employ 'temporary' stereogenic centres as stereodirecting groups to create remote stereocentres using substrate-directable reactions. For example, we have recently reported a three-step aldol/directed cyclo-propanation/*retro*-aldol protocol for the asymmetric synthesis of chiral cyclopropane carboxaldehydes in good ee (Fig. 2).[3] In this approach, a chiral auxiliary fragment **4** reacts with an α,β-unsaturated aldehyde **5** to afford a *syn*-aldol product **6** (Step 1), whose 'temporary' β-hydroxyl functionality is then used to control facial selectivity in a directed cyclopropanation reaction to afford cyclopropane **7** in very high de (Step 2). *retro*-Aldol cleavage of cyclopropane **7** results in destruction of the 'temporary' β-hydroxyl stereocentre, affording the chiral auxiliary fragment **4**, and the desired enantiopure cyclopropane carboxaldehyde **8** in high de (Step 3).

It was proposed that the excellent diastereoselectivity observed for cyclopropanation of *syn*-aldol **6** might also be exploited to devise a stereoselective synthesis of grenadamide **1** using the *retro*-synthetic analysis outlined in Figure 3. Therefore, grenadamide **1** would be prepared from conjugate reduction of α,β-unsaturated

Keywords: *syn*-aldol; Cyclopropanation; β-Elimination; Temporary stereocentre; Natural product.
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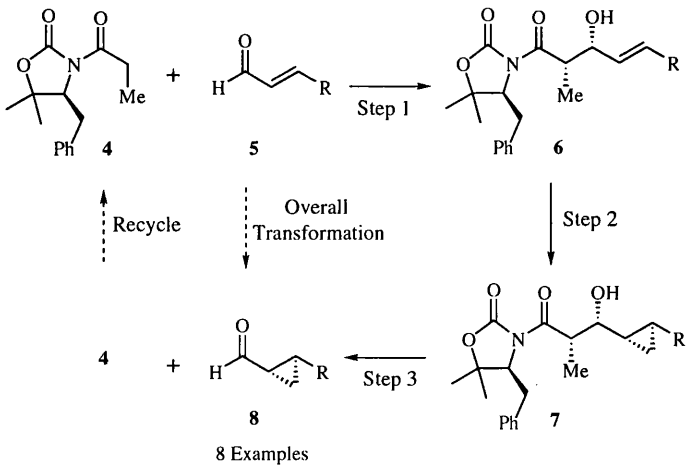


Figure 2. Aldol/cyclopropanation/*retro*-aldol strategy for the asymmetric synthesis of chiral cyclopropane carboxaldehydes.

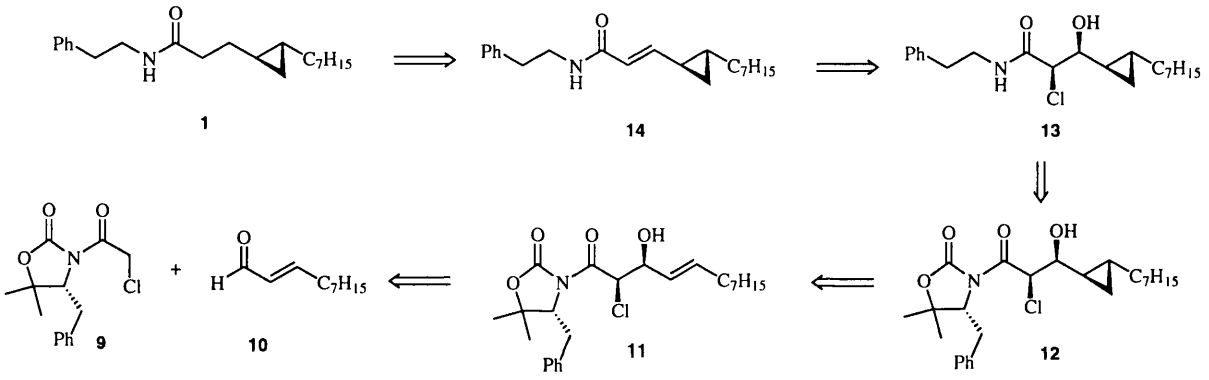
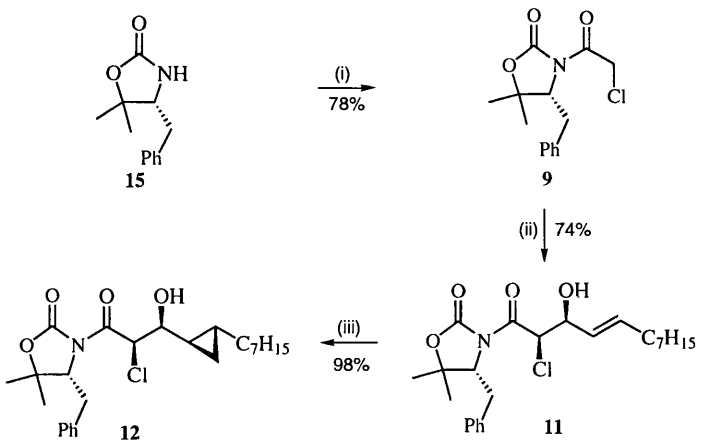


Figure 3. *retro*-Synthetic analysis of grenadamide **1**.

amide **14**, which could be derived from β-elimination of α-chloro-β-hydroxy-cyclopropane **13**.[4] The benzylamide functionality of cyclopropane **13** would be introduced via direct aminolysis of the oxazolidin-2-one fragment of **12** using phenylethylamine as a nucleophile. The cyclopropane ring of **12** could be introduced stereoselectively via a hydroxyl directed cyclopropanation reaction on *syn*-aldol **11** that would be prepared from aldol reaction of the (*Z*)-boron-enolate of *N*-chloroacetyl-5,5-dimethyl-oxazolidin-2-one **9** with (*E*)-dec-2-enal **10**. This synthetic strategy would therefore afford enantiopure grenadamide **1** in five steps from *N*-chloroacetyl-oxazolidin-2-one **9** via a relatively straightforward synthetic protocol that should be readily amenable to the preparation of analogues of this natural product as required.

It was thought necessary to employ the (*Z*)-boron enolate of *N*-chloroacetyloxazolidin-2-one **11** in order to ensure good levels of stereocontrol in the *syn*-aldol reaction, since boron enolates of *N*-acetyl-oxazolidin-2-ones are known to undergo aldol reactions in poor de.[5] It should be noted, however, that the presence of the α-chloro-substituent is essential for the subsequent β-elimination reaction of amide **13**, since it enables samarium diiodide to remove the β-hydroxyl functionality simultaneously, thus affording α,β-unsaturated amide **14** in a single step. It was decided to employ 'SuperQuat' oxazolidin-2-one **15** as a chiral auxiliary for this synthesis because the 5,5-dimethyl substituent would discourage nucleophilic attack of phenylethylamine at the endocyclic oxazolidin-2-one carbonyl of cyclopropane **12**, thus ensuring that this aminolysis reaction afforded amide **13** in good yield.[6]

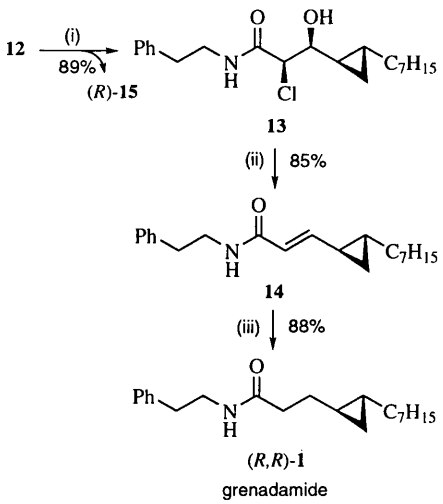
Our first task was to employ the *syn*-aldol/directed cyclopropanation methodology described in Figure 2 for the asymmetric synthesis of cyclopropane **12** in high de (Scheme 1). Therefore, (*R*)-4-benzyl-5,5-dimethyl-oxazolidin-2-one **15** was first prepared in 72% yield from unnatural D-phenylalanine using a previously reported procedure.[7] Treatment of (*R*)-**15** in THF at −78 °C with 1.1 equiv of *n*-BuLi, followed by addition of 1.1 equiv of chloroacetyl chloride gave α-chloroacetyl-oxazolidin-2-one **9** in 78% yield. Treatment of **9** with 1.1 equiv of 9-BBN-OTf and $^{i}Pr_2NEt$ in CH_2Cl_2 at 0 °C, followed by cooling to −78 °C and addition of (*E*)-dec-2-enal **10** resulted in *syn*-aldol **11** in 92% de, which was purified to >95% de in 74% yield via chromatography.[8] The *syn*-stereochemistry of aldol **11** was confirmed from the small $J_{(2',3')}$ coupling constant of 3.4 Hz observed in the ^1H NMR spectrum.[9] Reaction of *syn*-aldol **11** with 5 equiv of Et_2Zn and CH_2I_2 in CH_2Cl_2 at −10 °C, resulted in a highly stereoselective cyclopropanation reaction, to afford *syn*-cyclopropyl aldol **12** in >95%



Scheme 1. Reagents and conditions: (i) 1.1 equiv *n*-BuLi, THF, −78 °C; chloroacetyl chloride; (ii) 1.1 equiv 9-BBN-OTF, $^{i}Pr_2NEt$, CH_2Cl_2, 0 °C; (*E*)-dec-2-enal **10**, −78 °C; (iii) 5 equiv Et_2Zn, CH_2I_2, CH_2Cl_2, −10 to 0 °C.

de and in 98% yield.[10] Cyclopropanations under this type of modified Furukawa conditions are normally *syn*-selective due to minimization of $A^{1,3}$ strain in the transition state, and as a consequence the absolute configuration of **12** was assigned accordingly.[11]

With the key cyclopropane **12**[12] in hand it was then necessary to transform it into grenadamide **1** by replacing the oxazolidin-2-one fragment with phenylethylamine, and substituting both the α-chloro and β-hydroxy substituents for hydrogen atoms (Scheme 2). It was found that simply dissolving cyclopropane **12** in neat phenylethylamine resulted in a clean aminolysis reaction to afford 5,5-dimethyl-oxazolidin-2-one (*R*)-**15** and amide **13**,[13] which was isolated in 89% yield after chromatographic purification.[14] Analysis of the ^1H NMR spectrum and TLC of the crude product of this aminolysis reaction revealed no evidence of any side products arising from a competing endocyclic cleavage pathway. Previous work by Concellòn et al. had shown that



Scheme 2. Reagents and conditions: (i) phenethylamine, 25 °C; (ii) 3 equiv SmI_2, THF, 25 °C; (iii) 0.2 equiv $CoCl_2$, MeOH/THF (2:1), 25 °C; 4 equiv $NaBH_4$, DMF.

treatment of α-halo-β-hydroxy-amides with 3 equiv of SmI_2 resulted in clean elimination reactions to afford (*E*)-α,β-unsaturated amides in high de.[15] Therefore, treatment of α-chloro-β-hydroxy-amide **13** with SmI_2 in THF at room temperature resulted in β-elimination to afford (*E*)-α,β-unsaturated amide **14**[16] in 85% yield. Analysis of the ^1H NMR spectrum of the crude reaction product revealed no evidence of any of its (*Z*)-isomer having been formed in this reaction. Finally, treatment of vinyl-cyclopropane **14** with $NaBH_4$ and 20 mol % of $CoCl_2$ in MeOH/THF,[17] resulted in conjugate reduction of its alkene functionality to afford grenadamide **1**[18] as a white crystalline solid in 88% yield. Comparison of the spectroscopic details with that reported previously for grenadamide (*R,R*)-**1** ($[\alpha]_D^{25}$ −11.0, (*c* 1.0, $CHCl_3$); Lit.[1] $[\alpha]_D^{25}$ −11.0 (*c* 0.1, $CHCl_3$)) revealed that the correct enantiomer of the natural product had been prepared in enantiopure form.

It should be noted that the synthetic strategy described for the synthesis of grenadamide **1** represents a powerful approach for the asymmetric synthesis of natural products that contain remote stereocentres. The strategy employed relies on the use of a chiral auxiliary to generate a 'temporary' stereocentre that then acts as a stereodirecting group to relay stereochemical information via a substrate-directable reaction. This approach is synthetically powerful because it has the potential to afford chiral products that contain new stereocentres which are remote to the chiral auxiliary fragment, creating chiral building blocks that are often difficult to access using conventional synthetic approaches. We anticipate that this new type of 'chiral relay' strategy will prove applicable to the combination of other types of chiral auxiliary and substrate-directable reactions, thus enabling the asymmetric synthesis of other classes of natural product that contain remote stereocentres.

In conclusion, we have demonstrated the asymmetric synthesis of grenadamide **1** in six steps from 5,5-dimethyl-oxazolidin-2-one **15** in an overall 38% yield. The use of this methodology is currently under investigation for the synthesis of debromogrenadadiene **2** and

grenadadiene **3**, since both these natural products should be available from the common intermediate **12**.

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12. (*R*)-4-Benzyl-3-[(2′*R*,3′*S*)-2′-chloro-3′-((1″*R*,2″*R*)-2″-heptylcyclopropyl)-3′-hydroxy-propionyl]-5,5-dimethyl-oxazolidin-2-one **12**: $[\alpha]_D^{25}$ +11.0 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz): δ 0.40 (1H, m, *cyc*-CH_2), 0.61 (1H, m, *cyc*-CH_2), 0.79 (1H, m, *cyc*-C*H*), 0.85 (3H, t, *J* 6.8 Hz, CH_3), 0.90 (1H, m, *cyc*-C*H*), 1.12–1.29 (12H, m, CH_2), 1.32 (3H, s, CH_3), 1.36 (3H, s, CH_3), 2.61 (1H, br s, O*H*), 2.87 (1H, dd, *J* 14.3, 9.8 Hz, CH_AH$_B$Ph), 3.20 (1H, dd, *J* 14.3, 3.4 Hz, CH$_A$$H_B$Ph), 3.40 (1H, dd, *J* 7.9, 3.2 Hz, C*H*OH), 4.48 (1H, dd, *J* 9.8, 3.4 Hz, C*H*N), 5.78 (1H, d, *J* 3.2 Hz, C*H*Cl), 7.17–7.32 (5H, br m, Ar-*H*); δ_C ($CDCl_3$, 75 MHz): δ 10.8 (CH_2), 14.0 (CH_3), 16.6 (CH), 21.7 (CH), 22.3 (CH_3), 22.6 (CH_2), 28.6 (CH_3), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.8 (CH_2), 33.4 (CH_2), 34.6 (CH_2), 60.6 (CH), 64.2 (CH), 75.1 (CH), 83.0 (C), 126.9 (CH), 128.7 (CH), 129.0 (CH), 136.4 (C), 151.8 (C=O), 168.3 (C=O); ν_{max} (film)/cm^{-1}: 3500, 2924, 2854, 1770, 1716, 1605; MS (ES^+) 467.2668 ($[M+NH_4]^+$, $C_{25}H_{40}ClN_2O_4$ requires 467.2671).
13. (2*R*,3*S*)-2-Chloro-3-((1′*R*,2′*R*)-2-heptyl-cyclopropyl)-3-hydroxy-*N*-phenethyl-propionamide **13**: mp 64–65 °C; $[\alpha]_D^{25}$ −23.0 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz): δ 0.39 (1H, m, *cyc*-CH_2), 0.59 (1H, m, *cyc*-CH_2), 0.70 (1H, m, *cyc*-C*H*), 0.87 (3H, t, *J* 6.8 Hz, CH_3), 0.88 (1H, m, *cyc*-C*H*), 1.13–1.34 (12H, m, CH_2), 2.83 (2H, t, *J* 7.2 Hz, CH_2Ph), 3.49 (2H, m, NCH_2), 3.55 (1H, m, C*H*OH), 4.43 (1H, d, *J* 2.3 Hz, C*H*Cl), 6.77 (1H, br s, N*H*), 7.18–7.34 (5H, br m, Ar-*H*); δ_C ($CDCl_3$, 75 MHz): δ 11.3 (CH_2), 14.6 (CH_3), 17.2 (CH), 22.3 (CH), 23.0 (CH_2), 29.7 (CH_2), 29.8 (2 × CH_2), 32.2 (CH_2), 33.8 (CH_2), 35.8 (CH_2), 41.5 (CH_2), 64.9 (CH), 76.3 (CH), 127.0 (CH), 129.0 (CH), 129.2 (CH), 138.8 (C), 168.3 (C=O); ν_{max} (KBr)/cm^{-1}: 3277, 2921, 2856, 1647, 1557; MS (ES^+) 366.2198 ($[M+H]^+$, $C_{21}H_{33}ClNO_2$ requires 366.2194).
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18. 3-((1′*R*,2′*R*)-2′-Heptyl-cyclopropan-1-yl)-*N*-phenethyl-propionamide (grenadamide) **1**: mp 46–47 °C; $[\alpha]_D^{25}$ −11.0 (*c* 1.0, $CHCl_3$) (Lit.[1] $[\alpha]_D^{25}$ −11.0, *c* 0.1, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz): 0.16 (2H, m, *cyc*-CH_2), 0.38 (2H, m, 2 × *cyc*-C*H*), 0.87 (3H, t, *J* 6.8 Hz, CH_3), 1.14 (2H, m, CH_2), 1.24–1.33 (10H, m, CH_2), 1.49 (2H, m, CH_2), 2.18 (2H, t, *J* 7.5 Hz, CH_2CO), 2.81 (2H, t, *J* 6.8 Hz, PhCH_2), 3.52 (2H, q, *J* 6.8 Hz, CH_2NH), 5.51 (1H, br s, N*H*), 7.17–7.34 (5H, br m, Ar-C*H*); δ_C ($CDCl_3$, 75 MHz): 12.2 (CH_2), 14.5 (CH_3), 18.6 (CH), 19.3 (CH), 23.1 (CH_2), 29.8 (CH_2), 29.9 (CH_2), 30.0 (CH_2), 30.7 (CH_2), 32.3 (CH_2), 34.5 (CH_2), 36.1 (CH_2), 37.3 (CH_2), 40.9 (CH_2), 126.9 (CH), 129.0 (CH), 129.2 (CH), 139.3 (C), 173.5 (C=O); ν_{max} (KBr)/cm^{-1}: 3308, 2920, 2850, 1638, 1547; MS (ES^+) 316.2637 ($[M+H]^+$, $C_{21}H_{34}NO$ requires 316.2635).